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Paul Gross

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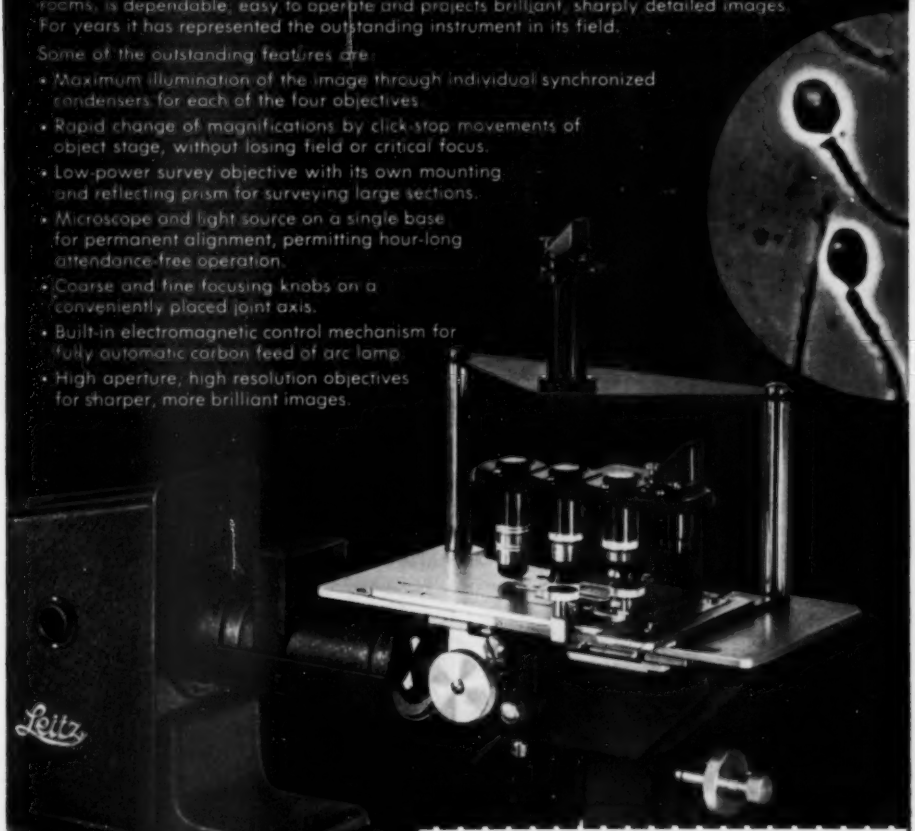
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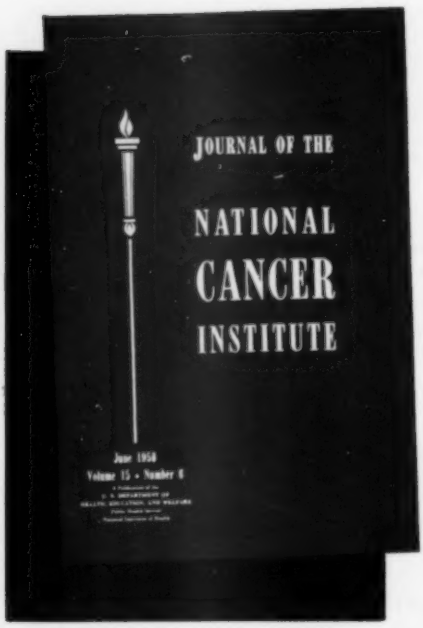
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The Perivascular Spaces in the Lung

PAUL GROSS, M.D., Pittsburgh

The perivascular space, sometimes also called perivascular "lymph" space, plays an important role in the present concept of the pneumoconioses. Within the perivascular space, according to some writers, lie the lymphatic vessels which are the migrational goal of the dust-filled alveolar macrophages. According to other writers the perivascular space *is* the lymphatic channel to which dust-containing alveolar macrophages electively migrate.

The theory has it that dust-filled alveolar macrophages are arrested within perivascular space *en route* to a lymphatic vessel or that they obstruct the lymphatic vessel within the perivascular space or the perivascular "lymph" space by their sheer number. The perivascular "lymph" space may thus become the site of a dust depot or of a silicotic nodule.

In routine examinations of lung sections it was noted that some blood vessels were surrounded by perivascular spaces, whereas other vessels of similar structure and size were not. Also, the percentage of vessels with perivascular spaces varied from one lung to the next.

The purpose of this communication is to demonstrate that the perivascular space is a pathologic entity rather than a normal structure.

Method and Materials

Rats and guinea pigs exposed to quartz dust in inhalation chambers and rats given intratracheal injections of quartz dust were killed at various intervals. The lungs of these animals as well as of those animals which had died of intercurrent disease were inflated with Bouin's solution.

The lungs of rats and guinea pigs raised under germ-free conditions and killed by a combination of cardiac puncture and decapitation under pentobarbital (Nembutal) anesthesia were similarly prepared.*

Sections were stained with hematoxylin and eosin and were also impregnated with silver for reticulin fibers by the method of Gordon and Sweet. In addition, many of the lung sections from animals exposed to quartz dust were studied by the incineration technique recently published.[1]

Results

In the lungs of animals raised under germ-free conditions the reticulum of alveolar walls abutting on blood vessels was generally tightly approximated either to the adventitia of the blood vessel or to the wall of a clearly defined lymphatic vessel interposed between the adventitia and the alveolar wall. In a few sections a split was demonstrable between some of the periadventitial fibers representing the beginning of a perivascular space. Some blood vessels of moderate size did not have demonstrable perivascular lymphatic vessels, and here the alveolar walls seemed tightly approximated to the adventitia of the blood vessel over the entire circumference.

The lymph vessels were generally prominent; the lumen, distended, and the wall,

Submitted for publication April 30, 1958.

From Industrial Hygiene Foundation, 4400 5th Ave. (13). Research Pathologist.

* Mr. Bruce Phillips, of the National Institutes of Health, and Dr. Helmut A. Gordon, Associate Research Professor of Lobund Institute, University of Notre Dame provided these lungs.

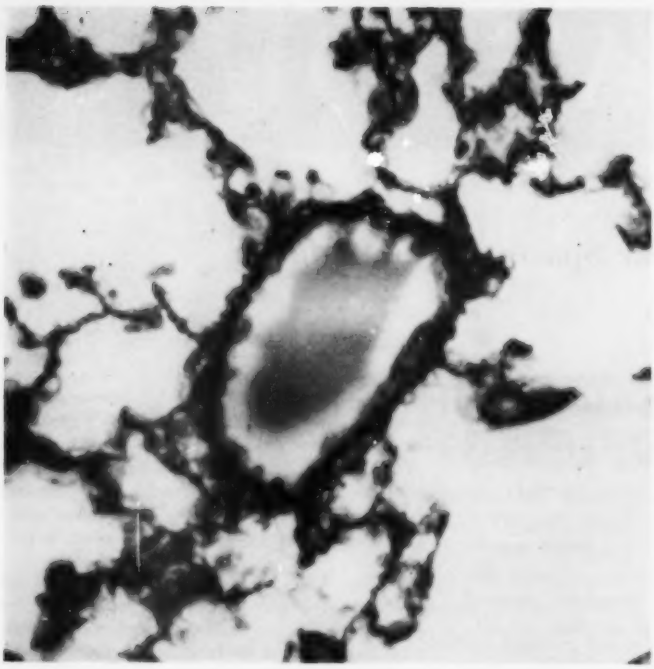


Fig. 1.—A small pulmonary vein from a guinea pig, 380 days old, raised under germ-free conditions. The alveolar walls abutting the vessel are tightly approximated to the vascular adventitia except for several foci marked *E*, where minimal edema has caused separation of the alveolar membrane. Gordon and Sweet method for reticulin fibers counterstained with Van Gieson's stain; reduced about 10% from mag. × 560.

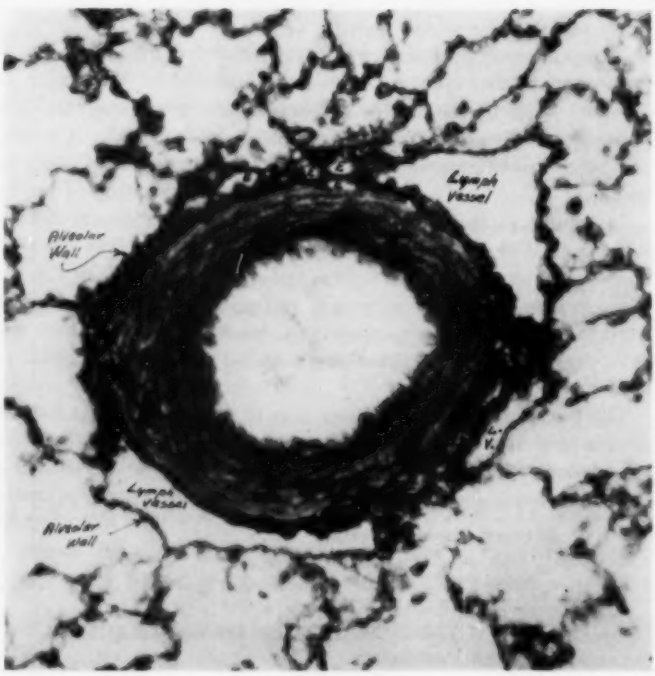


Fig. 2.—A small pulmonary artery from a guinea pig, 408 days old, raised under germ-free conditions. The lymph vessels are clearly defined and surround only segments of the arterial circumference, and the lymphatic lumens contain no fibrils. The alveolar walls abutting the artery are tightly approximated to the arterial adventitia except where lymph vessels are interposed. There is the beginning of perivascular edema, represented by small spaces *E* in the adventitial tissues. Gordon and Sweet method for reticulin fibers counterstained with Van Gieson's stain; reduced about 10% from mag. × 390.

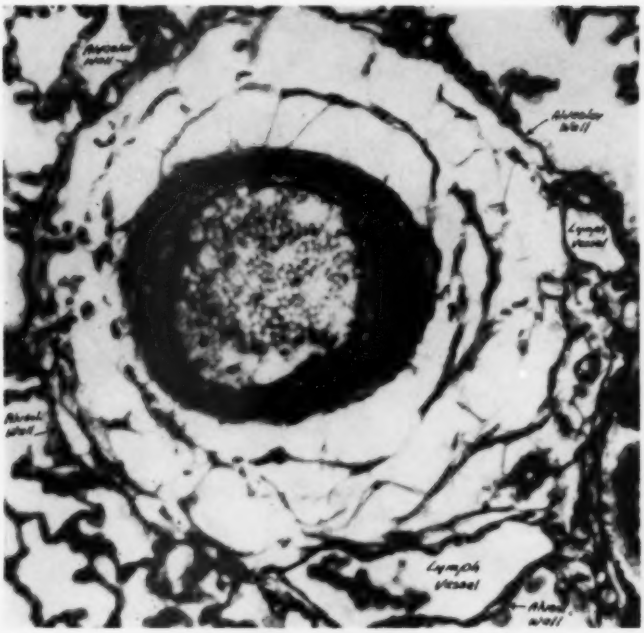


Fig. 3.—A small pulmonary artery from a rat killed with ether following four and one-half months' exposure to quartz dust in an inhalation chamber. There is here a large perivascular space, the outer limit of which is outlined by the reticulin of the abutting alveolar walls. The space contains fibrils, generally concentrically arranged, and a few cells. Several clearly defined lymph vessels are interposed between the perivascular space and abutting alveolar walls. It is to be noted that the perivascular space completely surrounds the blood vessel like a tire or doughnut, which lymph vessels do not do. Gordon and Sweet method for reticulin fibers counterstained with Van Gieson's stain; reduced about 10% from mag. × 390.

readily identified. Since the perivascular lymphatic vessel generally had an oval shape, a spiral course about the blood vessel was indicated. Most blood vessels demonstrated two to four lymphatic vessels. Occasionally a single lymphatic vessel partially enveloped a blood vessel like a horseshoe. No instance was found where a lymphatic vessel formed a complete uninterrupted circle, like a doughnut, about a blood vessel.

In animals given intratracheal injections of quartz dust or exposed to it in inhalation chambers the pulmonary blood vessels were frequently surrounded by an edematous zone which was recognizable as such by the fact that it contained widely separated fibrils more or less circumferentially arranged. These fibrils were part of the outer adventitia. There appear to be at least three important criteria by which a zone of perivascular edema differs from perivascular lymphatic vessels: (1) the absence of a definite endothelial lining, (2) the presence of fibrils in the presumptive lumen, (3) the continuity of the perivascular zone, which completely surrounds the blood vessel like a moat without the benefit of a drawbridge.

It is perhaps superfluous to add that it is this zone of perivascular edema which has been termed the perivascular space and the perivascular "lymphatic" space. These perivascular spaces may be partially occupied by a variable number of lymphocytes and monocytes (histiocytes, macrophages). It is characteristic of such perivascular space that the cellular infiltrate lies within a space bounded internally by the adventitia of the blood vessel and externally by the reticulum of abutting air spaces.

Comment

The assumption has been heretofore that most silicotic nodules are formed within perivascular spaces (by an infiltration of dust-filled macrophages). This assumption, however, was recently shown to be in error with the failure to demonstrate a delimiting reticulin membrane external to the cell collection in most young peri- or paravascular silicotic nodules.[2] Nevertheless, rare silicotic nodules do form in the perivascular space.[2]

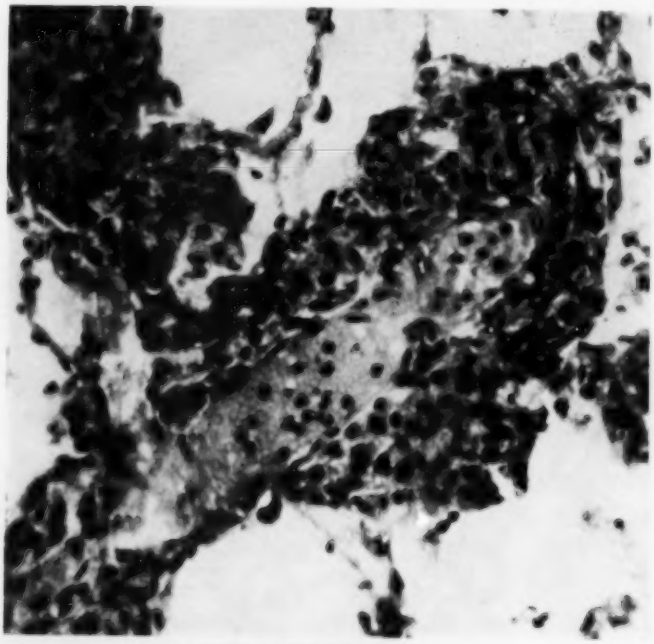


Fig. 4.—A perivascular cellular aggregation or nodule from a rat killel one month after an intratracheal injection of 47 mg. of quartz dust. Hematoxylin and eosin; reduced about 10% from mag. × 560.

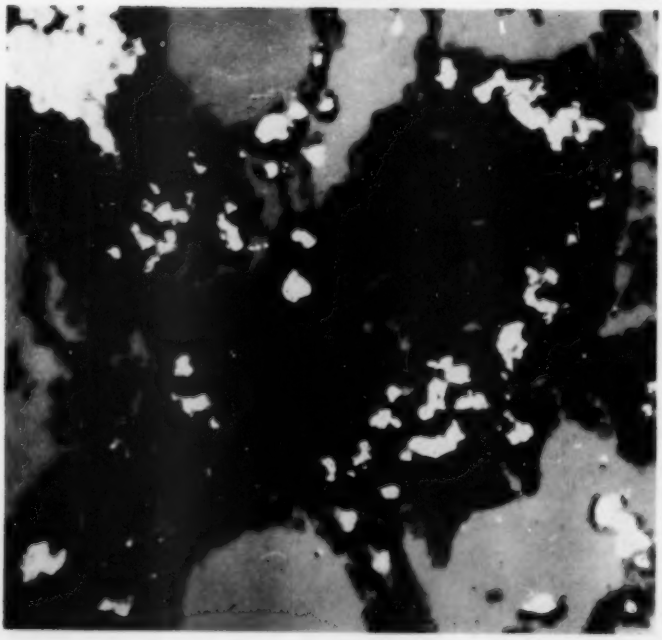


Fig. 5.—A composite photomicrograph of the same field as in Figure 4, showing the acid-insoluble ash content of the nodule, and thereby demonstrating its silicotic character. Reduced about 10% from mag. × 560.

It is probable that when the semipermeability of pulmonary vessels is impaired the blood plasma escaping from the lumen will exert pressure against the abutting alveolar walls. Since the counterpressure of the alveolar air is relatively insignificant, the

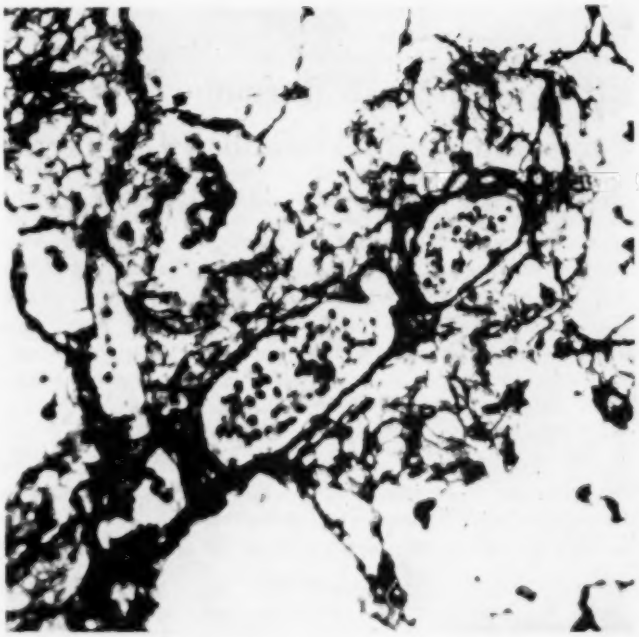


Fig. 6.—The same field as in Figure 4 after decolorization and silver impregnation for reticulin by the method of Gordon and Sweet. The absence of an outer delimiting membrane representative of the abutting alveolar walls proves that there is here no perivascular space. Furthermore, the fibers show more of a radial than a circumferential arrangement. It is also to be noted that no lymphatic vessel can be identified. Reduced about 10% from mag. × 560.

abutting alveolar walls are forced away from the vessel wall. In separating from the latter, however, the adherent adventitial fibers exert tension upon the remaining loose adventitial tissues, causing them to be pulled apart to give the resulting space its fibrillar content.

The misapprehension that the perivascular space is a normal anatomical structure is probably ascribable to its ubiquity in lung sections from routine autopsies and also from experimental animals where terminal pulmonary edema is very common. It is thought, however, that reflection upon the evidence here presented should bring about the recognition that the perivascular space is a pathologic entity. Also, it would appear that changes are indicated in the present concept regarding the mechanism by which dust is deposited about blood vessels, since this concept is predicated on the premise that perivascular spaces or "lymph" spaces are normal structures.

Summary

The pulmonary perivascular space is shown to be a pathologic entity, a perivascular edema, and not a normal anatomic structure.

A pulmonary perivascular space is not necessarily present about every blood vessel, and in the lungs of animals raised under germ-free conditions perivascular spaces may be nonexistent.

The relationship of lymphatic vessels to the perivascular space is clarified, and the impropriety of designating the latter as a perivascular "lymph" space is emphasized.

Miss Ethel B. Tolker prepared the slides.

Industrial Hygiene Foundation, 4400 5th Ave. (3).

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Effects of Growth Hormone on the Bone and Periodontium of Vitamin A-Depleted Rats

L. A. BAVETTA, Ph.D.; S. BERNICK, Ph.D., and B. H. ERSHOFF, Ph.D., Los Angeles

Considerable data are available indicating that various manifestations of nutritional deficiency are due not primarily to the deficiency per se but rather to an impaired production of various hormones which may result as a consequence of the deficient state (Morgan [1] and Ershoff [2]). In this regard, Bavetta et al.[3] recently observed that injections of growth hormone corrected the impaired chondrogenesis and osteogenesis of the tibia and alveolar bone of tryptophan-deficient rats, although such treatment was without significant effect on other manifestations of tryptophan deficiency, such as retardation in growth. In the present communication data are presented indicating that growth hormone administration was similarly effective in correcting the abnormalities in the bone and periodontium of rats depleted of vitamin A.

Submitted for publication March 25, 1958.

From the Departments of Biochemistry and Nutrition, University of Southern California School of Dentistry and School of Medicine.

Supported by a grant from the Office of Naval Research and from the Southern California State Dental Association. Communication No. 444 from the Department of Biochemistry and Nutrition, University of Southern California.

Procedure

The animals employed in the present experiment were female rats of the University of Southern California strain in which the dietary regimen of the mother rats was such as to make the young rats satisfactory for bioassay studies for vitamin A. The mother rats were maintained for at least two months previous to breeding and for seven days after birth of the litter on Sherman Diet B (Sherman-Campbell [4]) without addition of sup-



Fig. 1.—Proximal epiphyseal cartilage of tibia from an animal fed a vitamin A-free diet and given injections of saline. The epiphyseal cartilage is narrow as the result of decrease in the proliferating and hypertrophying layers. Note the osteoporosis of the diaphysis with an erythrocytic infiltration of the marrow spaces. *E.* indicates epiphysis; *E. P.*, epiphyseal plate; *DI.*, diaphysis. Mag. × 75.

plementary lettuce or meat. Litters were reduced to seven at 3 days of age, and on the seventh day mothers and litters were given a vitamin A-low diet.* The young rats were weaned at 21 days of age at an average body weight of 36 gm. Forty female rats from this group were selected for the following experiment.

Thirty rats were fed a vitamin A-free diet consisting of sucrose, 66%; casein,† 24%; salt mixture,‡ 5%; and corn oil, 5%. To each kilogram of the above were added the following vitamins: thiamine hydrochloride, 10 mg; riboflavin, 10 mg.; pyridoxine hydrochloride, 10 mg.; calcium pantothenate, 60 mg.; nicotinic acid, 100 mg.; ascorbic acid, 200 mg.; biotin, 4 mg.; folic acid, 10 mg.; p-aminobenzoic acid, 400 mg.; inositol, 800 mg.; cyanocobalamin (vitamin B_{12}), 150μg.; 2-methylnaphthoquinone, 5 mg.; choline chloride, 2 gm.; calciferol (vitamin D_3), 500 U. S. P. units; and alpha tocopherol acetate, 100 mg. The vitamins were incorporated in the diet in place of an equal amount of sucrose. Ten rats were fed a diet identical to the above but containing in addition 5000 U. S. P. units of vitamin A per kilogram of diet. Diets were made up weekly and stored under refrigeration when not in use. The animals were fed daily, and all food not consumed 24 hours after feeding was discarded. These measures were employed to minimize oxidative changes in the diet. The rats were housed in metal cages with raised screen bottoms (two or three animals per cage) and were provided with food and water ad libitum. The rats given the vitamin A-free diet were continued with this ration until they were depleted of vitamin A. The end of the depletion period was set as the fifth day on which rats given the vitamin A-free diet showed stationary or decreasing weight. The average time of depletion was 22 days after weaning (range, 18 to 24 days), and average body weight at time of depletion was 94 gm. (range, 67 to 118 gm.). Twenty-four of these animals ranging in body weight from 72 to 104 gm. were selected for the following experiment.

Animals were divided into two groups of 12 each and were treated as follows: One group received 10 daily intraperitoneal injections of 0.5 saline solution; the second group received 10 daily intraperitoneal injections of 0.5 ml. growth hormone§ solution containing 100μg. of growth

* Similar to U. S. P. XII depletion diet except that commercial casein rather than extracted (vitamin A-free) casein was employed.

† Vitamin-Free Test Casein, General Biochemicals, Inc., Chagrin Falls, Ohio.

‡ Hubbell, Mendel, and Wakeman Salt Mixture, General Biochemicals, Inc., Chagrin Falls, Ohio.

§ Beef STH (lot No. 728-074) was provided by Dr. Sanford L. Steelman of the Armour Laboratories, Chicago. This material had an activity of 90%-100% of Armour Standard. When assayed on hypophysectomized female rats, 15μg. to 20μg. of the above material per rat per day, according to Dr. Steelman, produced a gain of 1 to 1.5 gm. per day. The powdered hormone material was suspended in water and dilute alkali (NaOH), added to effect a solution. The volume was adjusted to a concentration of 200μg. per milliliter.

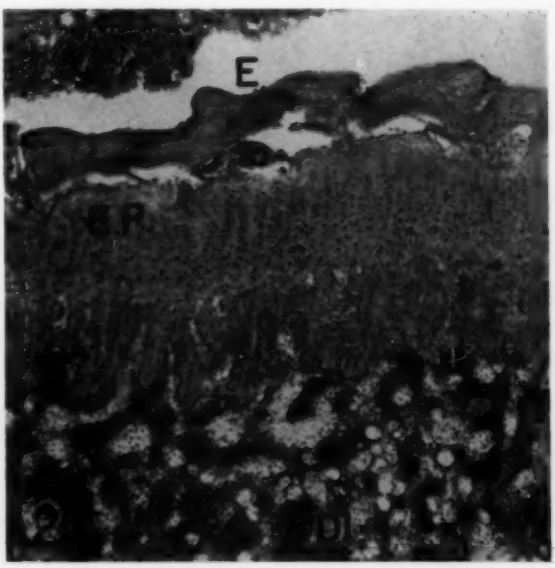


Fig. 2.—Proximal head of tibia from an animal fed a vitamin A-free diet and given growth hormone. There is an increase in the number of cells in both the proliferating and the hypertrophying layers. Note the reappearance of the myeloid elements in the marrow spaces. *E.* indicates epiphysis; *E. P.*, epiphyseal plate; *DI.*, diaphysis. Mag. ×75.

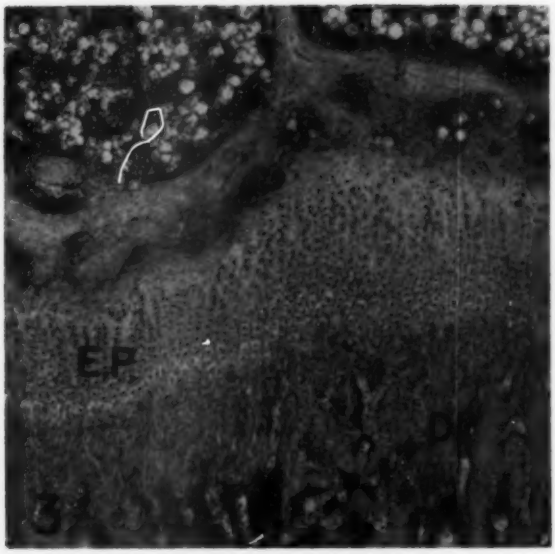


Fig. 3.—Proximal head of the tibia from an animal fed a vitamin A-free adequate diet. The epiphyseal cartilage width and architecture are normal for an animal of such an age. *E. P.* indicates epiphyseal plate; *DI.*, diaphysis. Mag. × 75.

hormone. During this period the vitamin A-free ration was continued. Surviving rats were autopsied 24 hours after the last injection. Animals which had received the vitamin A-containing ration were also autopsied at this time. The heads and tibias were removed at the time of killing and fixed immediately in an 80% alcoholic Bouin's (picric-acetic-formalin) solution. The specimens were decalcified in 10% nitric acid in 10% formalin and washed with a saturated lithium carbonate solution. They were then dehydrated and infiltrated in the routine manner, embedded in 50% nitrocellulose, sectioned at 20μ-30μ in thickness, and stained with hematoxylin and triosin.

Results

Nine of the saline-treated and seven of the hormone-treated animals survived until 24 hours after the last injection. In agree-

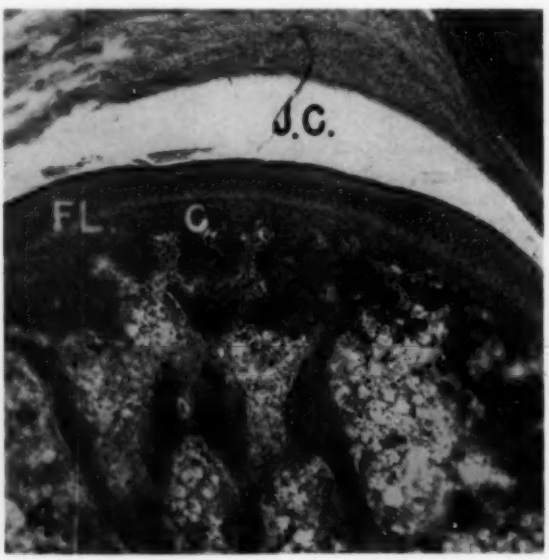


Fig. 4.—Mandibular condyle from an animal fed a vitamin A-free diet and given injections of saline. The cartilaginous zone is narrowed with a loss of trabeculae and myeloid elements in the ramus. *J. C.* indicates joint cavity; *F. L.*, fibrous layer; *C.*, cartilaginous zone. Mag. × 75.

ment with previous findings (Margitay-Becht and Wallner,[5] Ershoff and Deuel[6]), injections of growth hormone failed to promote an increment in body weight in rats depleted of vitamin A. No significant difference in body weight was noted between the saline-treated and hormone-treated animals (surviving rats in these groups lost an average of 3.9 and 3.7 gm., respectively, for the 10-day experimental period). Histologically, however, significant differences were observed between the two groups.

A marked narrowing of the epiphyseal plate was noted in the tibias of rats given saline (Fig. 1). This decrease in the width of the cartilaginous layer was the result of a decrease in the number and size of the cells making up the various layers. In addition there was a loss of bone trabeculae in both the epiphysis and diaphysis. The response of the epiphyseal plate of rats depleted of vitamin A and given growth hormone is illustrated in Figure 2. These animals exhibited an increase in chondrogenic activity in all the layers of the epiphyseal plate. The average width of the epiphyseal cartilage of the rats given saline injections was 190μ (Fig. 1); that of animals given the growth hormone was 295μ (Fig. 2). The epiphyseal plate of rats of comparable age which were given vitamin A continuously from weaning was 390μ (Fig. 3).

Differences in the periodontium and mandibular condyle were also noted between rats in the saline and in the growth-hormone series. Figure 4 represents a condylar section from an animal given saline injections. There has been a marked reduction in the number of cells composing the cartilaginous layer. The fibrous capsule appears very prominent. A few trabeculae persist in the ramus of the mandible, with a marked loss of myeloid elements. In contrast, the injection of growth hormone appears to stimulate chondrogenesis and osteogenesis, as seen in Figure 5. Additional evidence of stimulation is seen in the increased width of the cartilaginous layer, an effect very similar to that observed in the tibia. However, animals given the vitamin A-adequate diets exhibited condyles with a wider cartilaginous area and a denser bony structure (Fig. 6). The trabeculae are undergoing widening and enlargement, as indicated by the osteogenic tissue occu-



Fig. 5.—Mandibular condyle from an animal fed a vitamin A-free diet and given injections of growth hormone. Note the widening of the cartilaginous layer, with active osteogenic tissue and myeloid elements in the ramus. *C.* indicates cartilaginous zone; *F. L.*, fibrous layer; *J. C.*, joint cavity. Mag. ×75.

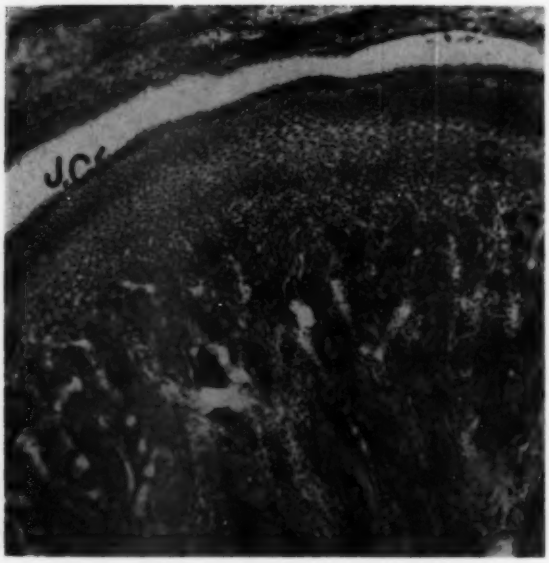


Fig. 6.—Mandibular condyle from an animal fed a vitamin A-adequate diet. Compare with Figures 4 and 5. Note the wide cartilaginous zone and thick trabeculae projecting into the ramus. *J. C.* indicates joint cavity; *F. L.*, fibrous layer; *C.*, cartilaginous zone. Mag. ×75.

pying the marrow spaces. The fat cells are again replaced by the myeloid elements.

In the periodontium, osteoporosis of the spongiosa of the interradicular region was present in all the rats of the saline group (Fig. 7). The cribriform plate and the adjacent periodontal membrane fibers, however, remained intact. In contrast, rats in the hormone-treated group exhibited bone deposition in the spongiosa of the interradicular bone, which largely obliterated the marrow spaces (Fig. 8). The appearance of the interradicular region of rats of a similar age which had been fed vitamin A from weaning is illustrated in Figure 9. The trabeculae of these animals were well developed, with marrow spaces filled with myeloid tissue.

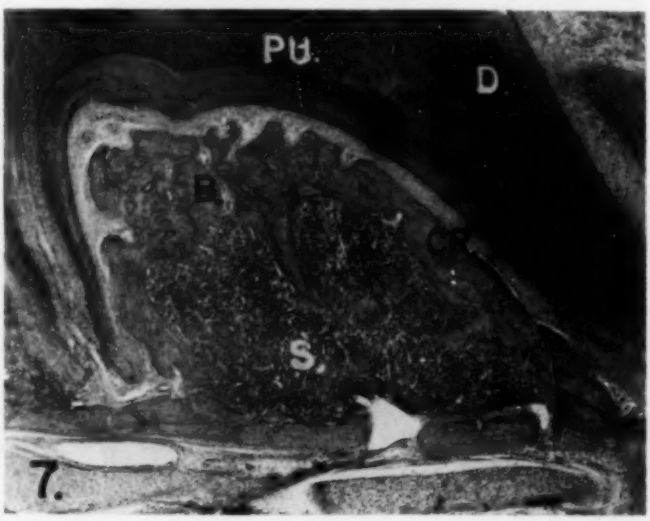


Fig. 7.—Upper first molar tooth from an animal fed a vitamin A-free diet and given injections of saline. Note the osteoporosis of the spongiosa of the interradicular bone. *PU.* indicates pulp; *D.*, dentin; *B.*, bone; *CR.*, cribriform plate; *S.*, spongiosa. Mag. ×75.

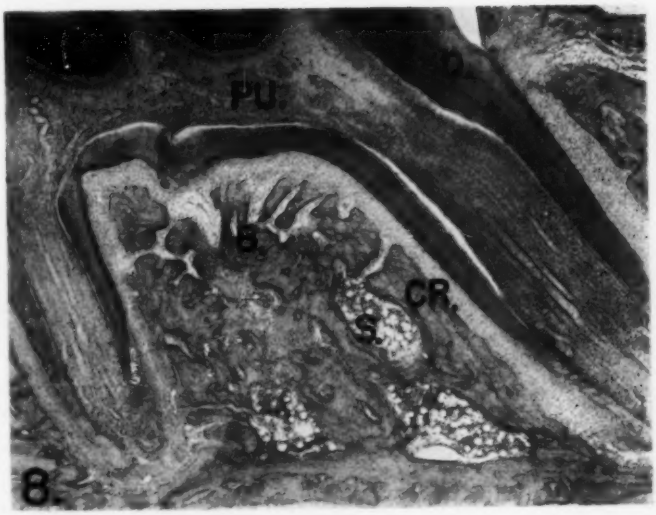


Fig. 8.—Upper first molar tooth from an animal fed a vitamin A-free diet and given injections of growth hormone. Note the wide anastomosing trabeculae of the spongiosa, with small marrow spaces. *PU.* indicates pulp; *D.*, dentin; *B.*, bone; *CR.*, cribiform plate; *S.*, spongiosa. Mag. ×75.

The incisal dentin of vitamin A-depleted rats given injections of saline is seen in Figure 10. The thin outer zone, homogeneous in nature, represents the dentin deposited preexperimentally, whereas in the wider middle zone the dentin formed during the experimental period is characterized by an abnormal number of interglobular spaces. In the innermost acidophilic zone the uncalcified predentin appears wider than normal. The incisal dentin of vitamin A-depleted rats given injections of growth hormone is seen in Figure 11. There is a marked decrease in the size and number of the interglobular spaces, with appearance of multiple equidistant incremental lines. These represent the response of the dentin to the 10 daily injections of growth hormone. In addition the width of the predentin is now normal. The incisor dentin from an animal given a vitamin A-adequate diet is seen in Figure 12.

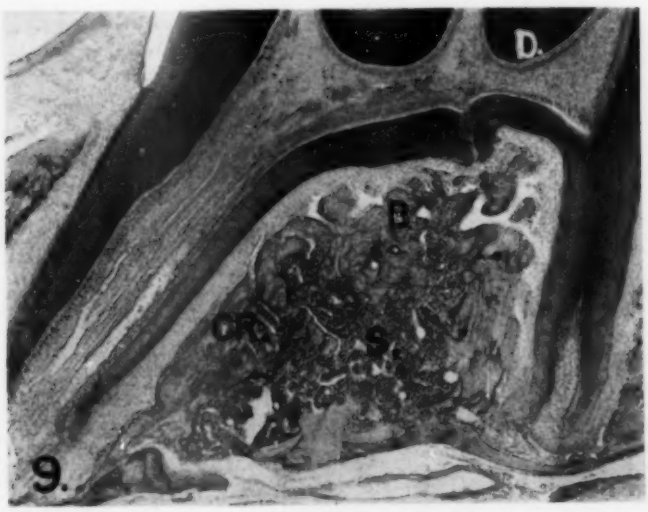


Fig. 9.—Upper first molar tooth from an animal receiving a vitamin A-adequate diet. Note the trabeculae and myeloid elements of the spongiosa. *D.* indicates dentin; *B.*, bone; *CR.*, cribriform plate; *S.*, spongiosa. Mag. ×75.

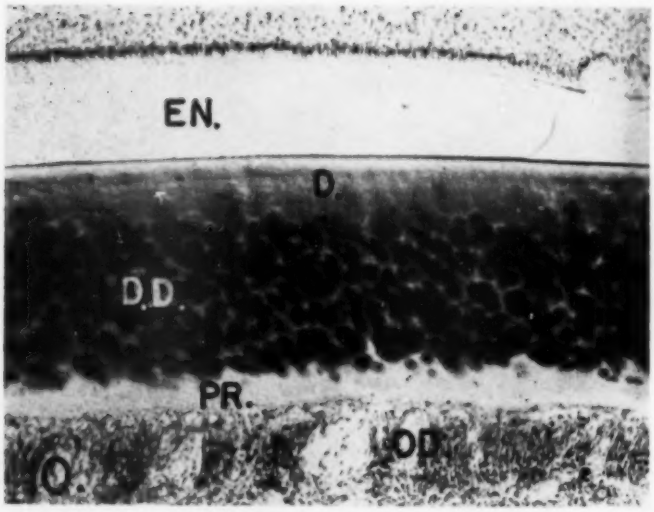


Fig. 10.—Incisal dentin from an animal fed a vitamin A-free diet and given injections of saline. Note the increase number of interglobular spaces and wide predentin. *EN.* indicates enamel; *D.*, dentin; *D. D.*, deficient dentin; *PR.*, predentin; *OD.*, odontoblastic layer. Reduced approximately 8% from mag. × 250.

Comment

Present findings indicate that rats depleted of vitamin A failed to respond to injected growth hormone by an increment in body weight but that such treatment did result in a stimulation in bone growth. These findings are in agreement with those previously observed in rats similarly treated but deficient in tryptophan (Bavetta et al.[3]). It is well recognized that the histopathological effects of a nutritional deficiency may be due either to (*a*) a deficiency of an essential nutrient in the tissue per se or (*b*) an insufficient supply of hormones or other metabolites which may result as a consequence of the deficiency. Present findings suggest that the impaired chondrogenesis and osteogenesis of the tibia and alveolar bone of rats depleted of vitamin A were due at least in part not to a vitamin A deficiency per se in these tissues but rather to an inadequate

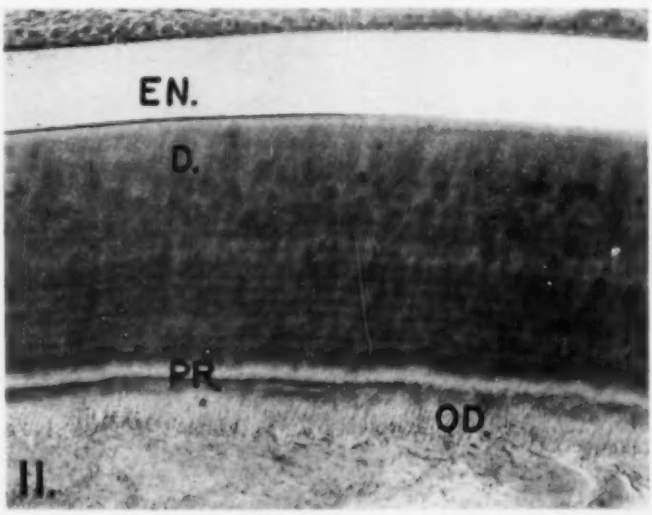


Fig. 11.—Incisal dentin from a vitamin A-depleted animal given growth hormone. Note the marked decrease in the number and size of the interglobular spaces and a reduction in the width of the predentin. Observe the incremental lines which represent the response of the dentin to the daily injections of growth hormone. *EN.* indicates enamel; *D.*, dentin; *PR.*, predentin; *OD.*, odontoblastic layer. Reduced approximately 8% from mag. × 250.

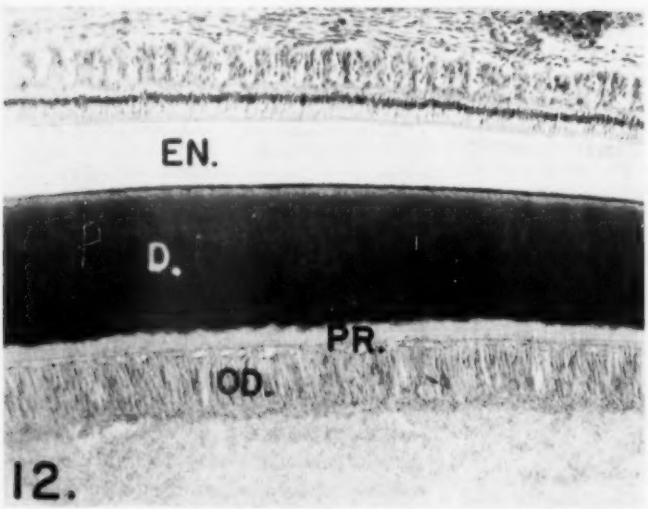


Fig. 12.—Incisal dentin from an experimental animal fed a vitamin A-adequate diet. Note the homogeneous nature of the dentin. *EN.* indicates enamel; *D.*, dentin; *OD.*, odontoblastic layer; *PR.*, predentin. Reduced approximately 8% from mag. × 250.

production or secretion of growth hormone which occurs as a consequence of vitamin A deficiency.

Summary

Administration of growth hormone failed to promote an increment in body weight in rats depleted of vitamin A. Growth hormone therapy, however, did cause a resumption of chondrogenesis in the epiphyseal region of the tibia, bone formation in alveolar bone, and the formation of normal-appearing incisal dentin. The suggestion is made that impaired chondrogenic and osteogenic activity in vitamin A-depleted rats is due, at least in part, to an inadequate production or secretion of growth hormone.

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Granulomatous Lesions—an Expression of a Hypersensitive State

An Experimental Study

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Introduction

The histopathology of the hypersensitive state has not been studied sufficiently. Though it became obvious early that the anaphylactic reaction occurs in "fixed tissue" [1] rather than in body fluids, the symptoms of anaphylaxis were regarded mostly as functional. Arthus [2] described the manifestations of the local response to foreign protein in 1903.[3] Biopsy specimens [4] taken from the experimental animal 24 and 48 hours after the shock injection demonstrated edema, leukocytic infiltrates, swelling of connective tissue fibers, and hemorrhages. Rössle [4] employed avian blood to provide an histologically demonstrable antigen. In the sensitized animal, absorption was slow and "defective," compared with controls; there was considerable local edema and a "tendency to hemorrhage." Later, lymphocytes and mononuclear cells appeared. Fröhlich [5] studied the allergic phenomena in the mesentery of the living frog. He observed stasis in the capillaries, edema, and swelling of nerve and connective tissue fibers; a barrier of leukocytes completely separated the site of injection from the general circulation. It is of interest that Abell and Schenck [6] made similar observations, 20 years later, with the transparent-chamber technique in rabbits. Gerlach [7] studied the Arthus phenomenon in different animals. The most responsive was the guinea pig, which manifested an early mobilization of histiogenic cells. Auer [8] observed the curious phenomenon of anaphylactic reaction in inflamed tissue at a distance from the site of application of the sensitizing or provoking injection. This principle was verified by Walsh and Cannon [9] and by Fox,[10] in direct demonstrations of a higher concentration of antibodies of such inflamed areas. Roulet [12] injected avian blood into the pleura of guinea pigs at five-day intervals; granuloma formation was observed after the eliciting injection; cells assumed a palisaded arrangement, and giant cells developed. Opie [11] studied the Arthus phenomenon in the skin of rabbits. The initial changes appeared five hours after the eliciting injection and were very much advanced after 48 hours. At this time, proliferation of the endothelial lining of lymphatics was observed, leading to the formation of multinucleated giant cells. Goddard,[13] in a detailed study of the histopathology of the hypersensitivity reaction to egg albumen in guinea pigs, found that mesenchymal elements react and proliferate after the provoking injection. The characteristic finding was a granuloma, related to nerves, adipose lobules, and capillaries, with or without giant cells. The elements which reacted were the endothelial and perithelial cells. The animals which received a nonspecific antigen as the shock injection had only residual inflammation, without endothelial or perithelial activity. Marsden and Morgan [14] consider an allergic mechanism in the production of granuloma. According to Forbus,[15] diseases in which immunity develops are characterized by granulomatous

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TABLE 1.—*Schedule of Sensitizing and Eliciting Injections in Test Animals and Controls*

Day	Experimental Animal	Control
0	1 ml. agg albumen intrap.	1 ml. egg albumen intrap.
	1 ml. egg albumen subcut.	1 ml. egg albumen subcut.
1	1 ml. egg albumen subcut.	1 ml. egg albumen subcut.
13	2 ml. egg albumen subcut.	2 ml. horse serum
14	2 ml. egg albumen subcut.	2 ml. horse serum
15	2 ml. egg albumen subcut.	2 ml. horse serum
16	2 ml. egg albumen subcut.	2 ml. horse serum
17	Biopsy	Biopsy
18	----	----
19	----	----
20	Biopsy	Biopsy

inflammation. Klemperer[16] considers the histiocytic granuloma a histologic phenomenon of the experimental allergic tissue reaction. Chase et al.[17] produced lesions of the skin in guinea pigs with use of killed bacilli of tuberculosis as adjuvants. They noticed a "familial" tendency to develop granulomatous nodules, with a higher frequency in females.

The present study was undertaken to ascertain the reproducibility of granuloma in the hypersensitive state.

Materials and Methods

Thirty guinea pigs, each approximately 250 gm. in weight, were given injections subcutaneously in the midabdomen of a 1% solution of crystalline egg albumen.* The amounts injected, the sequence of injections, and the intervals between injections are given in Table 1. Fifteen guinea pigs received crystalline egg albumen 13, 14, 15, and 16 days after the initial "preparing" injection, while the controls received on the same days horse serum subcutaneously. Biopsy specimens were taken from the skin at the site of subcutaneous swelling and were fixed in buffered 10% formalin. The slides were stained with hematoxylin and eosin. Biopsy specimens were obtained from two untreated guinea pigs for comparison (Fig. 1).

Results

Initially, three test and three control animals were used without attention to their sex (Table 1). On the day after the final shock injection the experimental animals had nodular masses in the subcutaneous tissue, causing thickening of the skin in plaque-like fashion. The controls had less extensive and thinner infiltrations of the skin. Biopsy specimens taken from the skin to the muscle layer were approximately 5 mm. thick and cut like ham in the experimental animals; the thickness was only 2-3 mm. in the controls. Three days later there remained a plaque of thickening in the animals treated with the specific antigen, while the controls presented a normal pliable skin, with mild infiltration of the suture line. New biopsy specimens were obtained from

* Obtained from the Emulsol Egg Products Corporation, 59 E. Madison St., Chicago.



Fig. 1.—Normal skin of guinea pig. Reduced about 40% from mag. ×70.

the experimental animals at a distance from the site of the previous biopsies to avoid the area involved in wound healing.

The biopsy specimens from the animals treated with horse serum demonstrated the following histologic findings: extensive edema; spaces filled with red blood cells; dilated capillaries and venules filled with blood cells, with predominance of leukocytes; leukocytic accumulations in perivascular position and in localized areas above the muscle (Fig. 14).

Biopsy specimens taken at the same time from the three animals treated with specific antigen also manifested conspicuous edema in the subcutaneous tissue. But there was also a proliferation of cells with vesicular nuclei of reticular, endothelial, and perithelial origin. There was proliferation of reticular cells in the fat lobules and in and above the muscle bundles. There were localized areas of leukocytic accumulations, in areas reticular cells tended to have a concentric arrangement, suggestive of granuloma.

In the biopsy specimens taken from the experimental animals on the 20th day after the first preparatory injection changes were more pronounced. A 5 mm. thick specimen again was removed from the experimental animals. The findings consisted of diffuse histiocytosis, forming a compact layer be-

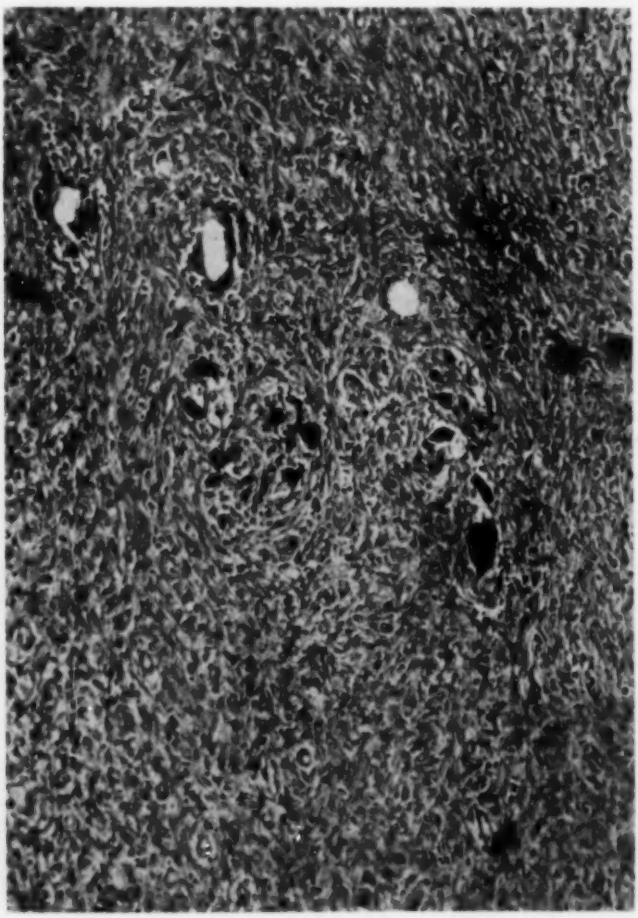


Fig. 2.—Guinea pig No. 1, sensitized with crystalline egg albumen. Biopsy specimen taken three days after shock injection. Granulomata with darkly stained giant cells; diffuse histiocytosis. Reduced about 10% from mag. × 170.

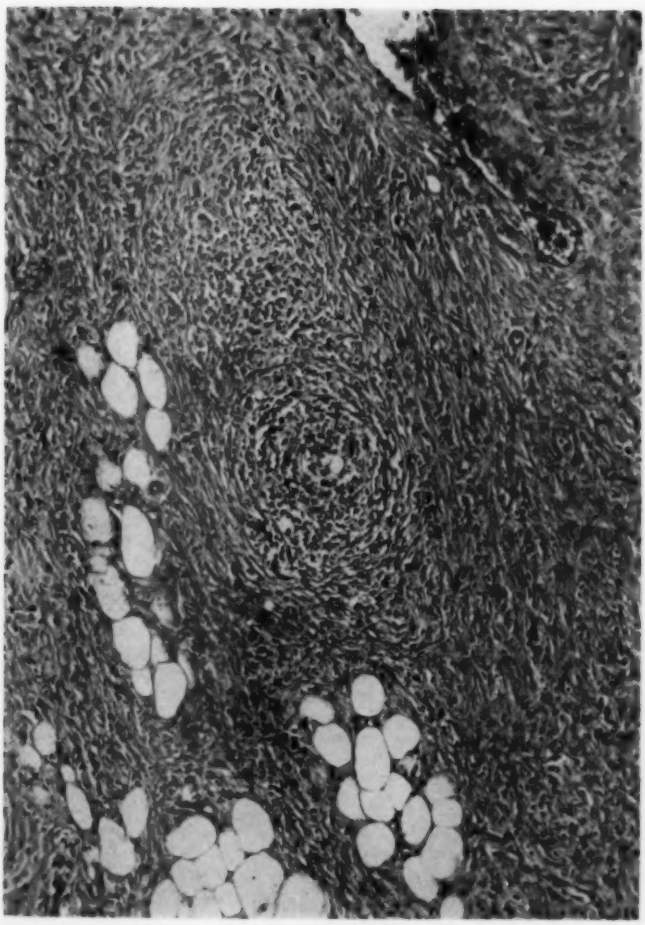


Fig. 3.—Guinea pig No. 1. Granulomata without giant cells around fat of subcutaneous tissue. Reduced about 10% from mag. × 160.



Fig. 4.—Guinea pig No. 2, sensitized with crystalline egg albumen. Biopsy specimen taken three days after shock injection. Granulomata with giant cells. Reduced about 10% from mag. × 160.

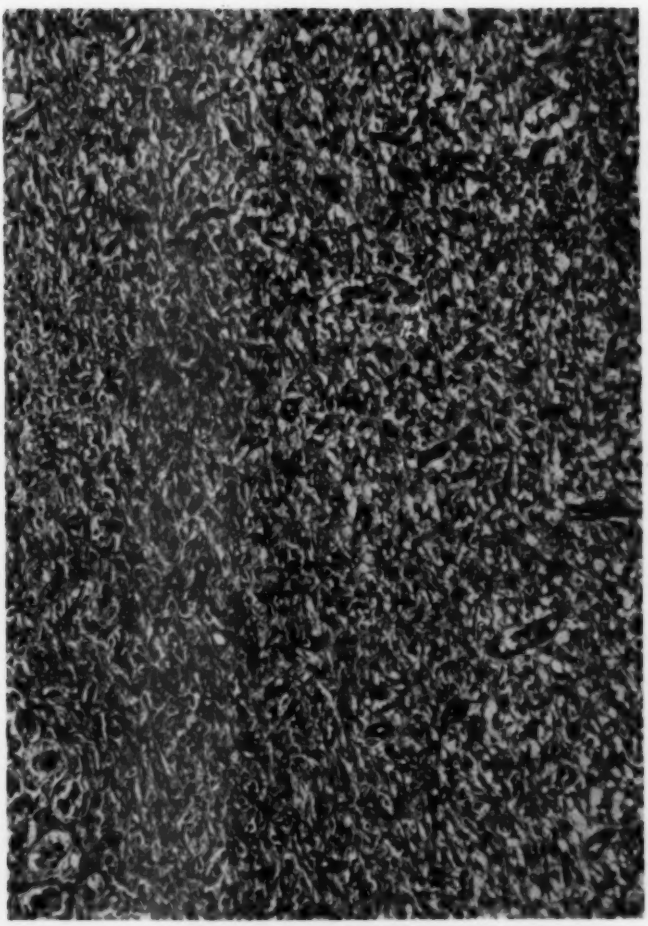


Fig. 5.—Guinea pig No. 3. Diffuse histiocytosis. Reduced about 10% from mag. × 200.

low the chorion and obliterating the fatty lobules; granulomata, with giant cells (Fig. 2) or without them (Fig. 3); few capillaries sprouting in the histiocytic newly formed tissue; some edema at the lower margin of the specimens, and areas of focal accumulation of leukocytes. Granulomata with giant cells again were found in the second animal (Fig. 4), while the third animal manifested diffuse histiocytosis without granuloma formation (Fig. 5); there were histiocytic proliferations in and above the muscle.

An additional 24 animals subsequently were treated similarly. Six males and six females received the specific antigen according to the original plan (Table 1); six males and six females received horse serum. Two female guinea pigs and one male died after the eliciting injection; the skin lesions were grossly more conspicuous and hemorrhagic in the females than in the males. Results of the surviving nine animals and their respective controls are listed in Table 2. Grossly, there was a typical Arthus reaction in the skin in two females, while a third female was pregnant and developed a dehiscence of the biopsy wound. No Arthus phenomenon was observed in the skin of the males, while a slight wound dehiscence was present in one male. Microscopically, the test animals manifested wide areas of diffuse histiocytosis, endothelial and perithelial proliferation (Fig. 6), granuloma formation (Fig. 7), and proliferation of fatty tissue trabeculae with giant-cell formation (Fig. 8). Cellular proliferation was particularly conspicuous around blood

TABLE 2.—*Gross Pathologic and Microscopic Findings in Test Animals and Controls*

		Guinea Pigs Treated with Specific Antigen		Guinea Pigs Given Another Injection of Nonspecific Antigen	
No.	Sex	Gross Pathologic Findings	Microscopic Findings	Gross Pathologic Findings	Microscopic Findings
1	—	Skin thick, with plaque of nodularities at site of injection	Diffuse histiocytosis in a compact layer; granulomata & giant cells	Slight thickening of skin around suture	Edema; spaces filled with erythrocytes; perivascular leukocytic accumulation
2	—	Skin thick, with plaque of nodularities at site of injection	Histiocytosis; diffuse leukocytic infiltr.; granuloma with giant cells	Slight thickening of skin around suture	Edema; spaces filled with erythrocytes; perivascular leukocytic accumulation
3	—	Skin thick, with plaque of nodularities at site of injection	Diffuse histiocytosis	Slight thickening of skin around suture	Edema; spaces filled with erythrocytes; perivascular leukocytic accumulation
4	♀	Died after eliciting injection	—	—	—
5	♀	Died after eliciting injection	—	—	—
6	♂	Died after eliciting injection	—	—	—
7	♀	Necrotic area with defect 1.5 cm. in diam.; Arthus phenomenon	Diffuse histiocytosis; endothelial & perithelial prolif.; perivascular infiltrates	Slight thickening of skin	Bands of fibrosis; edema
8	♀	Necrotic area with defect 1.5 cm. in diam.; Arthus phenomenon	Diffuse histiocytosis; granuloma formation; fatty tissue giant cells	Slight thickening of skin	Edema; occasional hemorrhage
9	♀	Pregnant; dehiscence of wound of 1st biopsy	Diffuse histiocytosis; endothelial proliferation; localized leukocytes	Slight thickening of skin	Edema; diffuse hemorrhagic infiltration
10	♀	Thick skin with plaque of nodularities	Diffuse histiocytosis	Slight thickening of skin	Edema; diffuse hemorrhagic infiltration
11	♂	Dehiscence of wound	Diffuse histiocytosis muscle atrophy	Skin thickened, edematous	Edema; perivascular accumulation of round cells
12	♂	Thickened edematous skin	Prolif. fatty-tissue trabeculae granuloma with giant cells	Normal thickness & pliable skin	Edema; perivascular round cells
13	♂	Thickened edematous skin	Diffuse histiocytosis	Skin thickened in plaque-like fashion	Diffuse histiocytosis foci of epithelial cells; multinucleated fibroblasts
14	♂	Thickened edematous skin	Diffuse histiocytosis; perivascular granulomas & perivascular cellular infiltrat.	Skin thickened in plaque-like fashion	Edema; hemorrhage
15	♂	Thickened edematous skin	Diffuse histiocytosis; prolif. of fatty-tissue trabeculae	Skin thickened in plaque-like fashion	Edema; hemorrhage

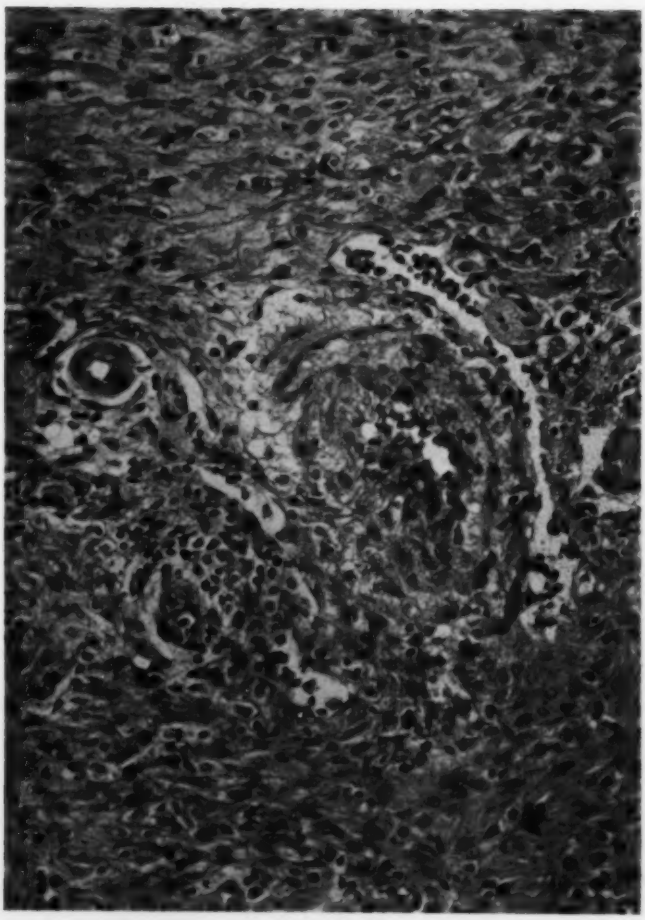


Fig. 6.—Female guinea pig No. 7, given another injection of specific antigen. Endothelial proliferation. Perivascular infiltration. Reduced about 10% from mag. × 290.

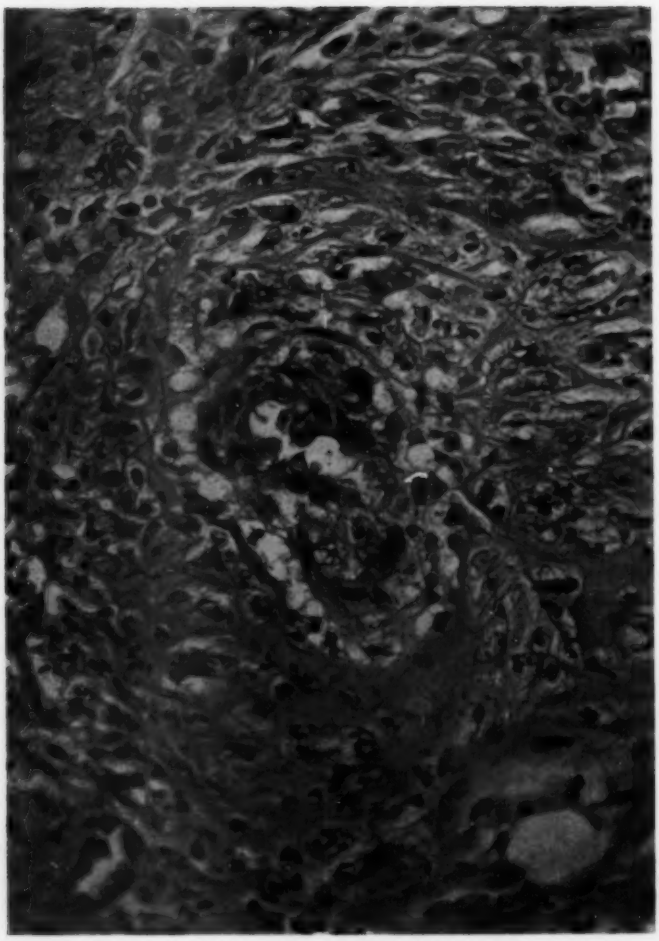


Fig. 7.—Female guinea pig No. 8, given another injection of specific antigen. Granuloma formation. Reduced about 10% from mag. ×475.

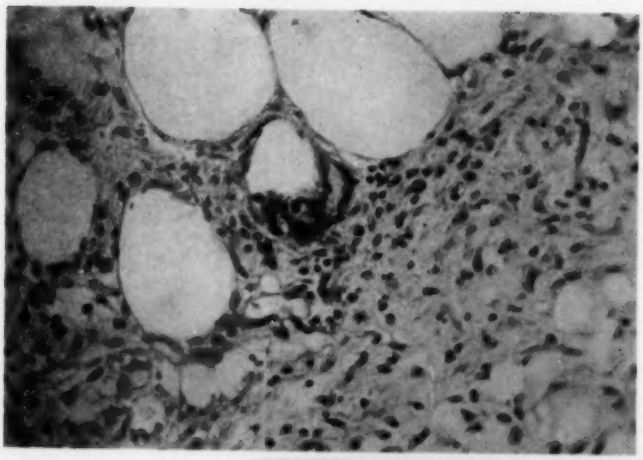


Fig. 8.—Female guinea pig No. 8, given another injection of specific antigen. Giant cells. Reduced about 40% from mag. × 500.

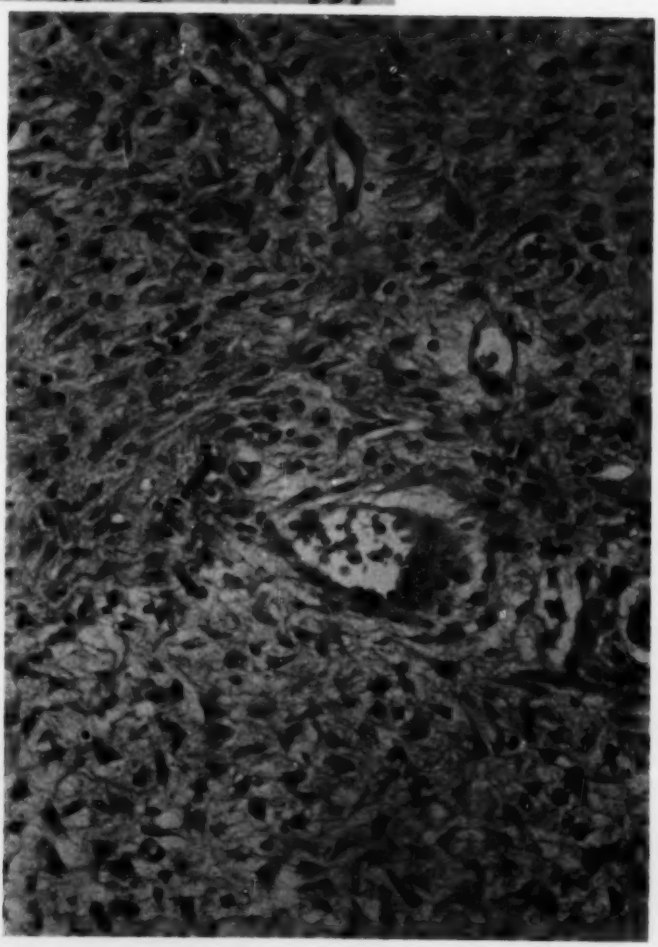


Fig. 9.—Female guinea pig No. 9, given another injection of specific antigen. Note endothelial proliferation. Reduced about 10% from mag. × 335.

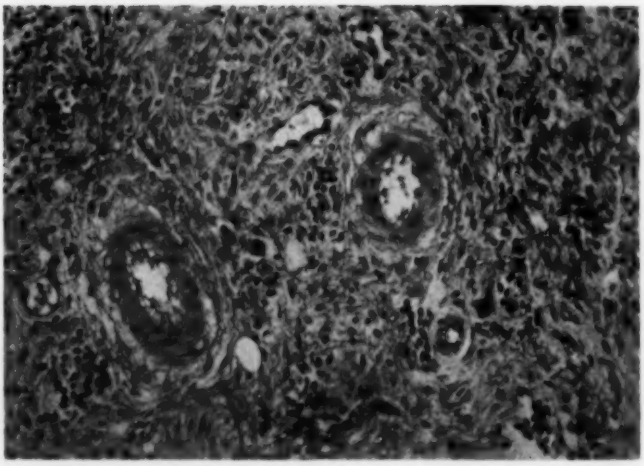


Fig. 10.—Male guinea pig No. 14, given another injection of specific antigen. Hyaline swelling of vascular wall and perivascular infiltration. Reduced about 40% from mag. × 305.

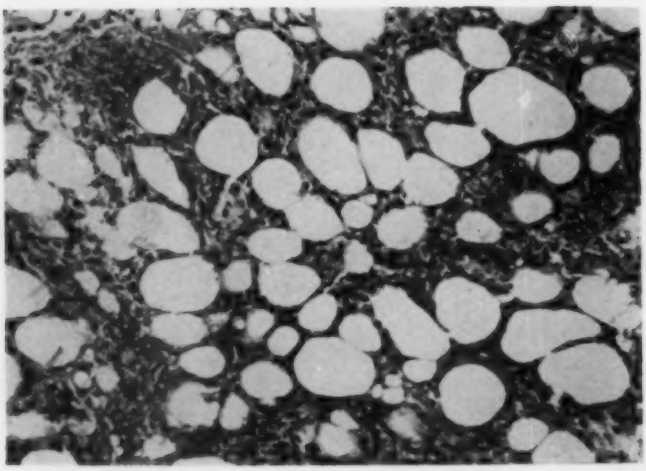


Fig. 11.—Male guinea pig No. 15, given another injection of specific antigen. Marked proliferation in the lobules of fatty tissue. Reduced about 40% from mag. × 245.

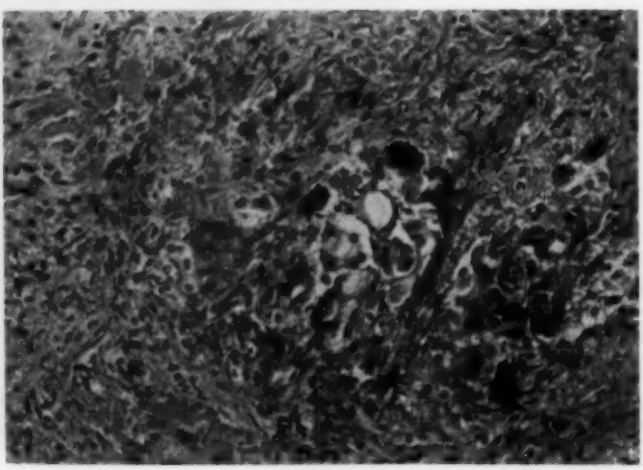


Fig. 12.—Male guinea pig No. 12, given another injection of specific antigen. Granulomata and giant cells. Reduced about 40% from mag. × 320.

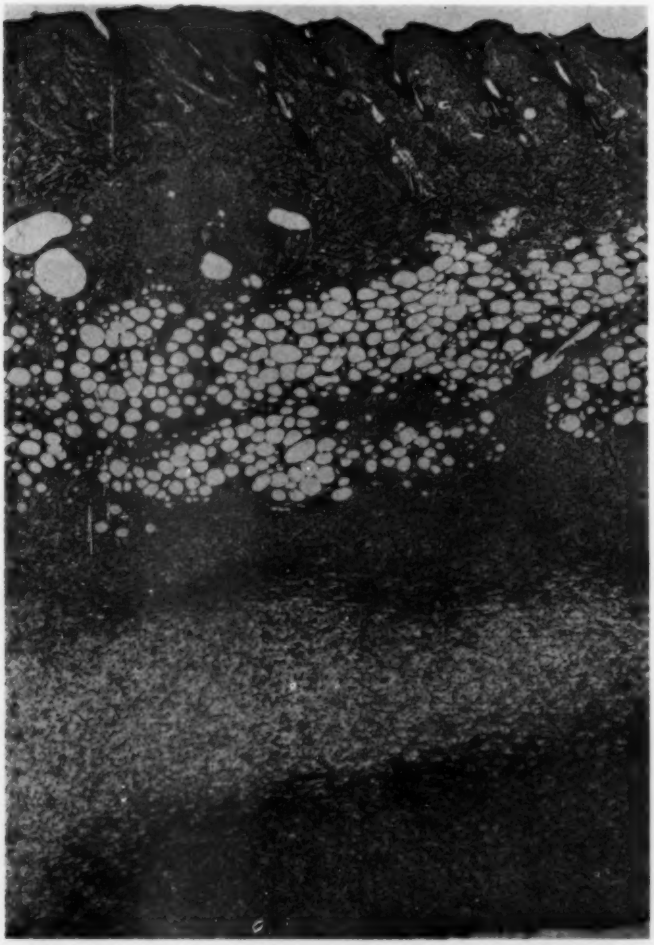


Fig. 13.—Female guinea pig No. 9, given another injection of specific antigen. Diffuse histiocytosis in adipose tissue and above muscle. Reduced about 10% from mag. × 35.

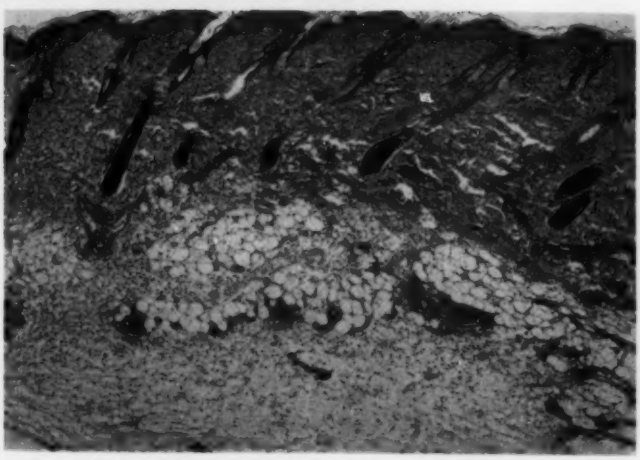


Fig. 14.—Male guinea pig, given another injection of nonspecific antigen. Reduced about 40% from mag. × 47.

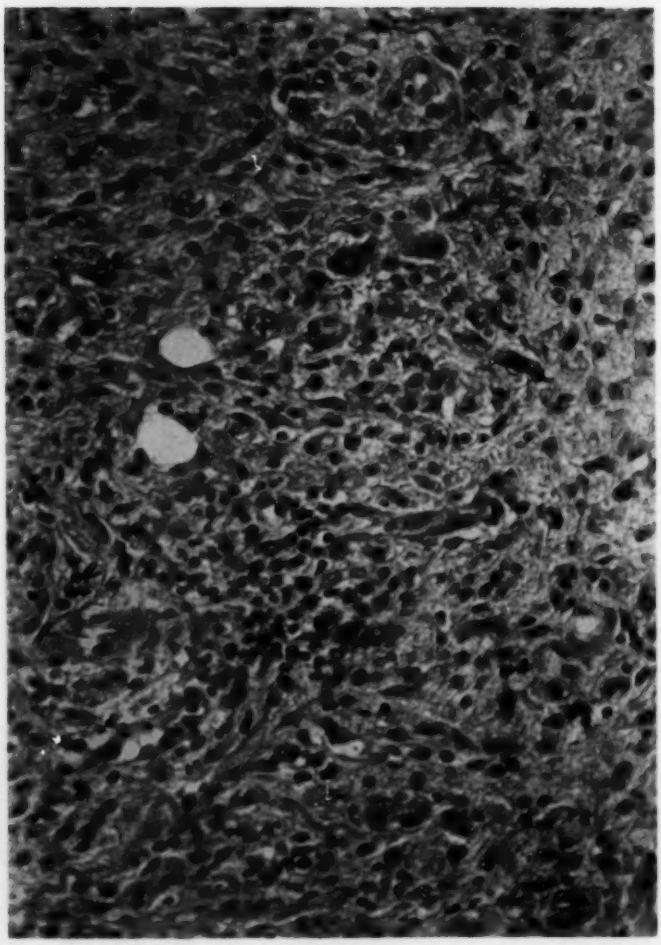


Fig. 15.—Male guinea pig, given another injection of nonspecific antigen, No. 14 control. Note granulomata with giant cells. Reduced about 10% from mag. × 365.

vessels (Figs. 9 and 10) and in and around fat lobules, leading to cellular masses around fatty cysts and to granulomas with giant cells (Figs. 11 and 12).

In the test animals eosinophils were abundant. Mostly diffuse, they gathered in foci around blood vessels and at the margin between proliferating reticular cells and fatty lobules (Fig. 16). The controls had only a few eosinophils scattered over wide areas and noticed only when specifically searched for. The difference between the typical picture seen in the sensitized animals and the controls is well shown in Figures 13 and 14. The only striking exception is the male guinea pig treated with horse serum and showing a diffuse histiocytosis and multinucleated fibroblasts (Fig. 15). This was the only case of a mesenchymal reaction with multinucleated cells in the control group (1 of 12), while granulomata with giant cells were found in 5 of 12 sensitized animals.

Blood was drawn four weeks after the first injection from four experimental animals † and from two untreated guinea pigs. Precipitins to crystalline egg albumen were

† Performed by Dr. E. Bregman, Ph.D., Department of Physiology, The University of Chicago.

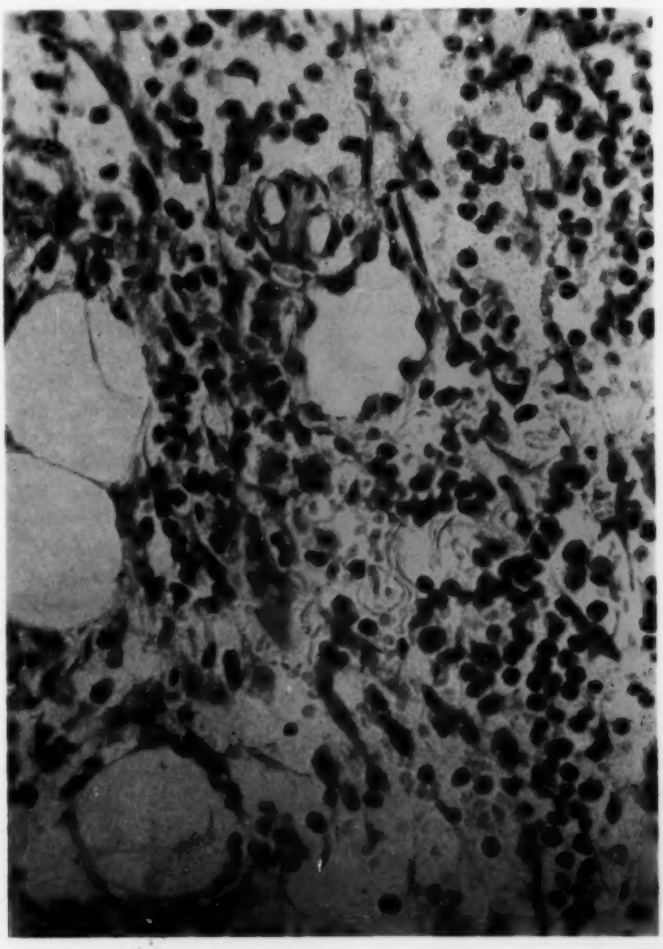


Fig. 16.—Tissue eosinophilia in sensitized guinea pigs. Reduced about 10% from mag. × 525.

present in the former and absent in the latter. These limited but representative tests confirmed the specificity of the sensitization, and additional tests were not considered necessary.

Comment

These results largely confirm the findings of Goddard [13] and of Chase et al.[17] concerning early mobilization of mesenchymal elements in the hypersensitive state, evolving into granulomata, with or without giant cells. In the controls there was only residual inflammation without signs of endothelial or perithelial reactivity. This latter finding is in accord with earlier work by Hartwich.[18] The rapid regression of this residual inflammation is noteworthy.

What of the single case of granuloma formation in the control group? No exceptions were found by Goddard [13] in experiments performed on guinea pigs, but no indication was given of the numbers of animals used or the percentage of single features of the pathological findings. Variations in responsiveness to hypersensitivity reactions are not unusual. Anaphylaxis is of relative specificity, a fact well known to Richet.[19] Bruynoghe [20] injected ox serum into guinea pigs; three of five animals died when given an eliciting injection of horse serum. Lesné and Dreyfus [21] observed that an increase in number of sensitizing injections would render the animal more susceptible to an eliciting dose of a nonspecific antigen. Gay and Southard,[22] in a special study of the specificity of anaphylaxis, found considerable differences in results, depending upon the amounts of antigen injected, the routes of administration, and the type of eliciting injection. In the present study, the animals had had repeated sensitizing injections and multiple eliciting injections, the last consisting of horse serum, especially powerful for eliciting purposes in Gay and Southard's hands. Occasional reactions following the application of a nonspecific antigenic stimulus, therefore, is not surprising. The single exception does not appear to invalidate the results obtained by Goddard.

Statistical analysis of the present data indicate that granulomatous lesions were significantly more frequent in the experimental animals, compared with the results in the control group ($P<0.05$). There was an amazingly large amount of eosinophils in the biopsy specimens of test animals and only single cells in the controls. Tissue eosinophilia has been noticed by many observers in sensitized animals. On repeated injections of a specific antigen into the peritoneal cavity, increased counts of eosinophils were obtained.[23] Only actively immunized animals manifest tissue eosinophilia. It is assumed by Speirs [24] that the eosinophilia is due to the presence of antigen and that these cells would represent the first stage in the production of antibody against the antigen.

What is the significance of granulomas and giant cells in human pathology? There are many conditions associated with granuloma formation; some have characteristic giant cells, not dissimilar from those produced in the hypersensitive animals. Tuberculosis is known for the Langhans type of giant cell; hypersensitivity plays a major role in the tuberculous infection.[25] Similar granulomata are found in sarcoidosis; Teilum [26] considers this disease an expression of morphologic immunologic reaction; granulomata, hyperglobulinosis, and paramyloid deposits would have a common allergic origin. The foreign-body giant cells with granuloma formation seem to differ from the allergic nature of granuloma, but the long incubation period needed for the production of beryllium granuloma may suggest some slow chemical action on cell protoplasm with phenomena of sensitization.[27] Granulomata with giant cells are found in the mesenteric nodes of Whipple's disease [28] ‡ and Puite [29] considers tissue hypersensitivity to mucoproteins a reasonable possibility in the pathogenesis of this disease. The local Arthus phenomenon

‡ Case from Albert Merritt Billings Hospital.

appears to result in granuloma formation [11-13,30] if observations are extended over a sufficient period of time. There are allergic states, on the other hand, not associated with the type of histopathology described in the local hypersensitivity reaction. Periarteritis nodosa is considered a manifestation of hypersensitivity,[31] and yet granulomata of the type noted in the present group of animals are not described in the experimental periarteritis lesions [32] or in the naturally occurring disease in man.[33] Nor were granulomata originally described in conjunction with the Shwartzman phenomenon [34]; nevertheless, granulomata with giant cells are found in serial biopsy [35] specimens taken from the colon of rabbits treated with a Shwartzman type of procedure.

It would appear that the presence of granulomas and giant cells should arouse suspicion of a hypersensitivity mechanism. Forbus,[36] also reviewing the circumstances of granuloma formation, assumes the possibility of a "specific factor or a pathogenic potential common to all."

Differences in the degree of hypersensitivity appear to be linked with sex in the present group of guinea pigs. Two of six females and one of six male guinea pigs died after the first eliciting injection. Locally, the reaction was more pronounced and somewhat hemorrhagic in the females. Two of four surviving females developed an Arthus phenomenon in the skin at the site of injections. One female underwent dehiscence of the operative wound. A similar dehiscence was observed in one of the five surviving males. No marked differences could be observed in the microscopical findings of the tissue response. No differences were observed in the minimal inflammatory changes among the male and female control animals. These few facts suggest that females may be more responsive to hyperimmune phenomena, as emphasized by Chase [17]; further study of this interesting question seems desirable.

Summary

Five of twelve sensitized guinea pigs, on the third day after the eliciting injection (crystalline egg albumen), developed granulomata, with or without giant cells. These animals and the others of the same group also manifested diffuse histiocytosis, endothelial and perithelial proliferation, and thickening of fatty-tissue trabeculae.

Only 1 of 12 animals given injections of a nonspecific antigen developed a significant mesenchymal reaction, with formation of multinucleated cells. Only edema and residual inflammatory changes were noted in the remaining 11 animals.

Conclusion

The granuloma, with or without giant cells, though not pathognomonic, is highly characteristic of the hypersensitive state in the experimental animal.

Department of Medicine, The University of Chicago.

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The Effect of Hyperoxia on Bone Resorption in Tissue Culture

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Introduction

There is still much uncertainty regarding the mechanism of bone resorption and the origin and function of the cells involved in this process. Further knowledge along this line may depend in part on the development of simple easily duplicated techniques capable of promoting bone resorption. To date, the use of parathyroid gland tissue or extracts has proven most valuable for the experimental production of this phenomenon.

Although the mode of action of parathyroid hormone is unknown, there is considerable evidence that it has a direct effect on bone. Indeed, the studies of Barnicot [1] and of Chang [2] have been considered, according to McLean,[3] as "the final and conclusive link in the chain of evidence." Barnicot demonstrated a local destructive action of parathyroid gland tissue on parietal bone *fragments* implanted intracerebrally in mice, and Chang obtained similar results with parathyroid glands grafted underneath the periosteum of the *intact* parietal bone of mice and rats. The specificity of this activity is notable, for in both studies the use of control transplants of other tissues placed in contact with bone failed to result in bone resorption. However, it is noteworthy that implants of crystalline vitamin A did have a similar destructive effect.[4] More recently, Gaillard [5] reported that in vitro cultivation of parathyroid gland tissue together with fragments of parietal bone from nearly full-term mouse embryos resulted in bone resorption within four days, while no resorption was evident in control fragments cultivated alone or together with another tissue, such as thyroid gland. The present communication deals with observations on the effect of hyperoxia on mouse calvaria in tissue culture and demonstrates a consistent and dramatic form of bone resorption independent of direct hormonal action.

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Department of Oral Pathology, Harvard School of Dental Medicine; U. S. P. H. S. Senior Research Fellow.

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Material and Methods

Whole calvariae were removed aseptically from 2- to 3-day old Swiss Albino mice of the Webster strain and placed in a Petri dish containing 100 units each of penicillin and streptomycin per milliliter of Gey's balanced salt solution.* Each calvaria was placed on a small rectangular coverslip and embedded in a plasma clot composed of 2 drops of heparinized chicken plasma plus 1 drop of chick embryo extract. The coverslip cultures were inserted within Leighton tubes, and to each culture was added 2 ml. of supernatant medium made up of Gey's balanced salt solution, 100 units of penicillin and streptomycin in Gey's balanced salt solution, 13- to 14-day chick-embryo extract, and heated horse serum[6] in a ratio of 5:1:2:2. Occasionally, four to five coverslip cultures were placed in large bottles containing 14 ml. of supernatant fluid. All experimental cultures were gassed with a mixture of 95% O_2 and 5% CO_2, whereas the control cultures were untreated or gassed with a mixture of 95% air and 5% CO_2. The initial pH within the gassed tubes was approximately 7.2.

* Obtained from Microbiological Associates, Bethesda, Md. Each liter contains NaCl, 8.0 gm.; KCl, 0.375 mg.; $CaCl_2$, 0.275 mg.; $MgCl_2 \cdot 6H_2O$, 0.210 mg.; $NaHCO_3$, 0.250 mg.; KH_2PO_4, 0.025 mg.; $Na_2HPO_4 \cdot 2H_2O$, 0.150 mg.; Glucose, 2.0 gms.

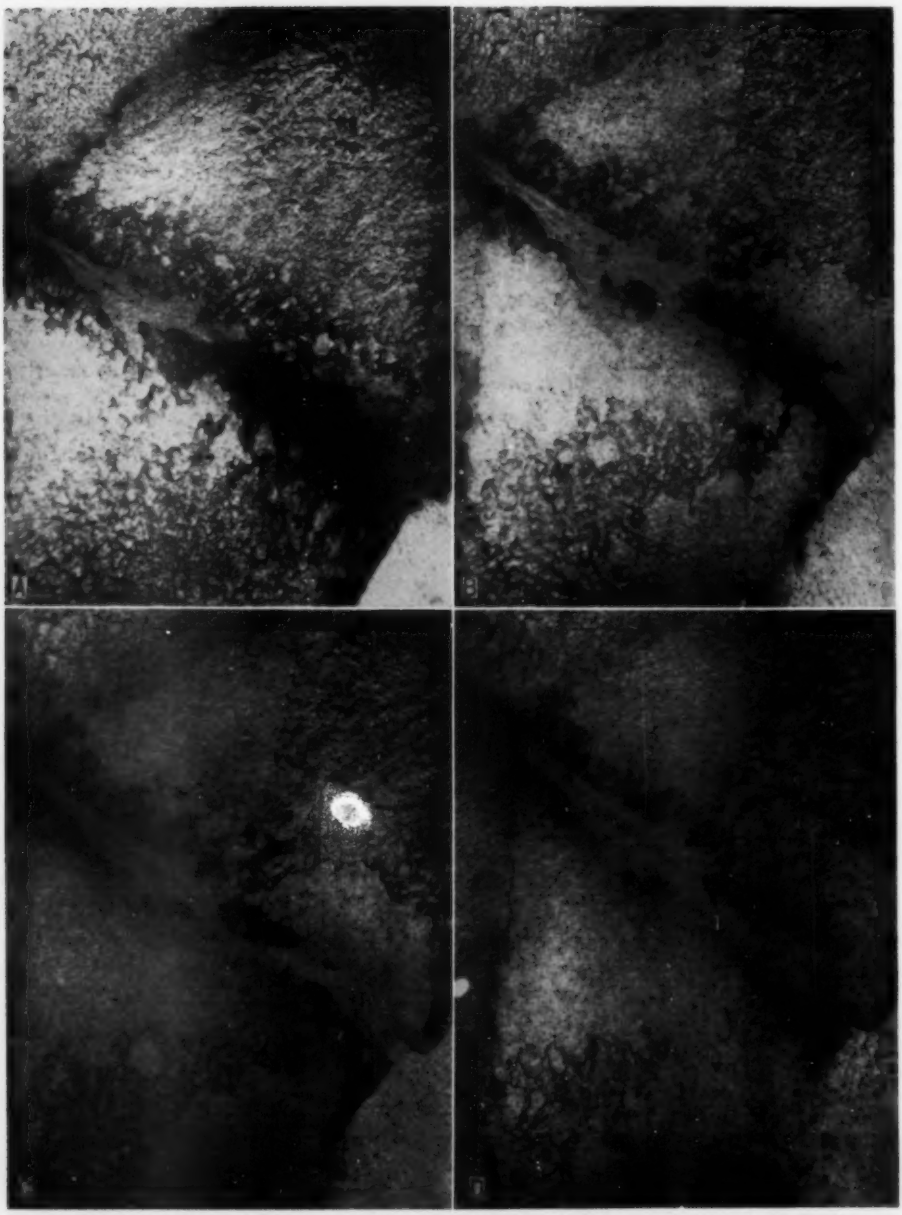


Fig. 1.—*A*, 2-day-old culture of mouse calvaria, exposed to hyperoxia, showing resorption of bone under way around frontal suture. *B*, same culture (3 days old), showing rapid progression of bone resorption within one day. *C*, same culture (4 days), continuing bone resorption. *D*, same culture (5 days), showing resorption of most of frontal bone. Reduced 40% from mag. ×45.

Following the displacement of air within the culture vessel by bubbles of supernatant fluid raised by the gassing procedure, the tubes were stoppered and placed in an incubator at 37 C. The cultures were examined microscopically daily and were refed and gassed every 2 days for periods up to 12 days.

Results

The tissue cultures of young mouse calvariae subjected to 95% O_2 and 5% CO_2 in the gas phase routinely exhibited rapid bone resorption, frequently recognizable as early as one day after cultivation. Initially, the resorption process was most prominent within the frontal bone near the heavily calcified area adjacent to the median suture. The typical rapid progression of bone destruction is illustrated in Figure 1. By the fifth day of cultivation the bone in the region of the frontal suture was almost completely resorbed and the process had spread laterally to involve most of the frontal bone. The parietal bone was affected as well. The earliest sign of activity in this area was the appearance of small "holes" within the bone. These gradually enlarged and coalesced during the next several days until typical scalloped areas of resorption were readily visible throughout the explant.

Observations with time-lapse cinematography (× 100 magnification) revealed marked cellular activity, particularly of macrophages, within the resorbing explants. Although typical osteoclasts were not readily distinguishable in the living cultures, histological examination revealed their presence within three days after cultivation (Fig. 2). By the sixth day, the resorptive process had slowed down considerably and the explant appeared more dense and opaque. In the older cultures, the most striking histological difference between control fragments from ungassed cultures or those gassed with 95% air and 5% CO_2 (neither procedure produces bone resorption) and the oxygenated cultures was the sparsity of cells and progressive degenera-

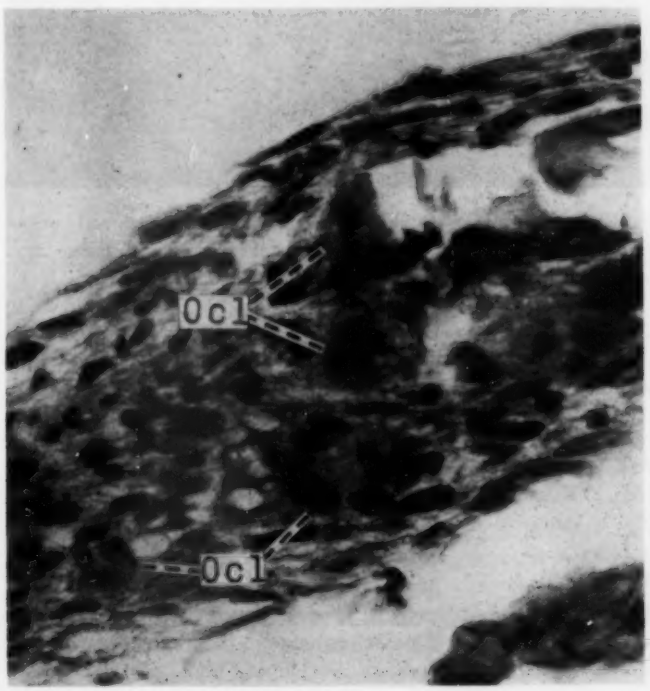


Fig. 2. — Histological section of 3-day-old culture, exposed to hyperoxia, showing numerous multinucleated osteoclasts. Note the prominent marginal vacuoles within the two lower osteoclasts. *Ocl* indicates osteoclast; reduced 10% from mag. × 645.

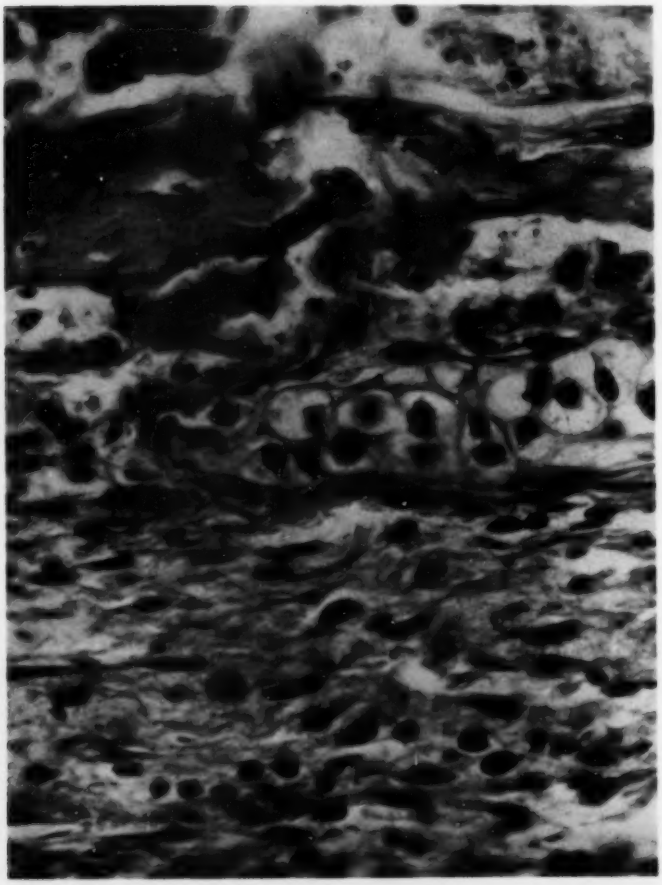


Fig. 3. — Histological section of 10-day-old *ungassed* culture. Note degenerating cartilage and sparsity of cells. Reduced 10% from mag. ×645.

tion within the former explants (Fig. 3). By comparison, the latter oxygenated explants (Fig. 4) showed an increased number of healthy viable cells.

Of further interest was the finding that explants exposed to high concentrations of oxygen maintained the additional capacity to form new bone after the initially rapid bone resorption had ceased. By 11 days, distinct areas of newly formed osteoid were found within the explants of many oxygenated cultures (Fig. 5).

Comment

The marked effects obtained with hyperoxia on whole mouse calvaria in tissue culture show a striking similarity to those found by Gaillard with combined organ cultures of parathyroid gland tissue and fragments of mouse-embryo parietal bone. Although early bone resorption seemed to take place without prominent osteoclastic activity, typical multinuclear osteoclasts were found shortly thereafter. In both studies, time-lapse microcinematography revealed large actively motile cells which appeared to be intimately associated with resorbing bone surfaces. Gaillard has described such cells as "osteoclasts," but according to our findings these particular cells may actually be large macrophages actively engaged in phagocytosis of bone spicules. This interpretation is in accord with the findings in vivo of "bone salt aggregates"

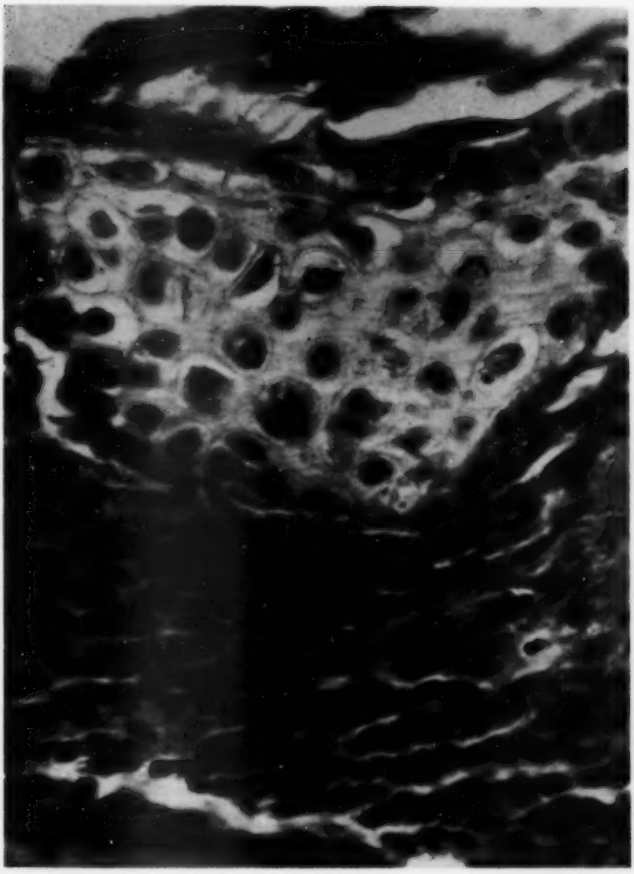


Fig. 4. — Histological section of 10-day-old culture exposed to hyperoxia. Note the large concentration of healthy viable cells. Reduced 10% from mag. × 645.

within macrophages during rapid bone resorption following large doses of parathyroid extract.[7] However, in view of the transformation of monocytes in tissue cultures into macrophages, epithelioid cells, and multinucleated giant cells [8] and the possible formation of osteoclasts by the fusion of precursor wandering cells,[9] it is conceivable that both cell types are interrelated.

The variability in response of different areas of the calvaria to hyperoxia may possibly be related to the in vivo distribution and activity of osteoclasts and macrophages, or their precursors, at the start of the experiment. Barnicot, using vital staining with neutral red, has shown that as the parietal bone increases in size the osteoclasts spread over a larger area and then thin out in the central region.[10] Although it has been suggested that the differentiation and multiplication of osteoclasts occurs in response to a primary action on the bone salt or matrix, our findings suggest a direct effect of hyperoxia on the bone-resorbing cells or their precursors. In either case, it seems clear that the process of bone resorption involves marked cellular activity. It is tempting to speculate that both hyperoxia and parathyroid hormone similarly modify metabolic pathways, thereby resulting in increased cell metabolism and the local accumulation of substances responsible for bone resorption.

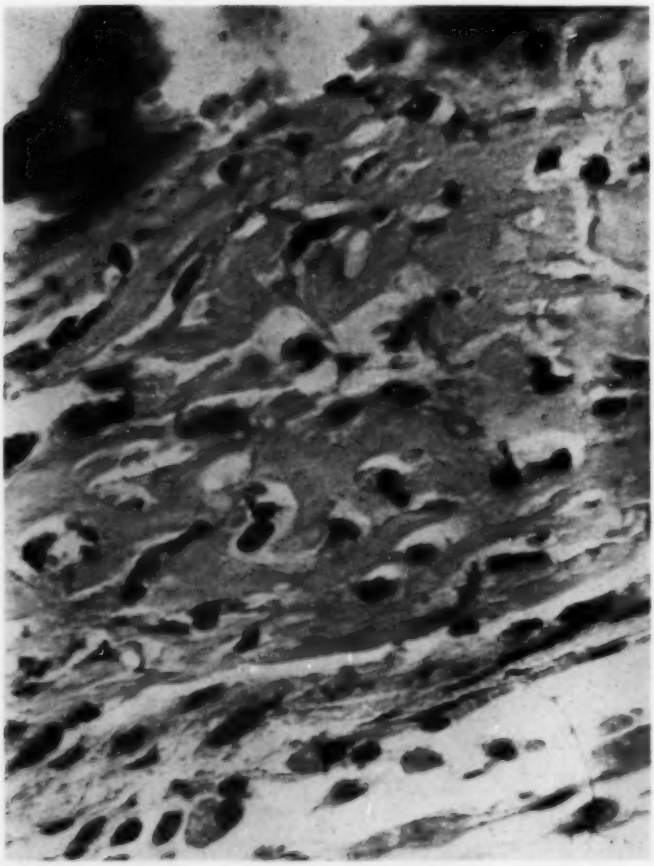


Fig. 5. — Histological section of 11-day-old culture exposed to hyperoxia. Note the broad band of newly formed osteoid. Reduced 10% from mag. × 645.

In the living animal, the effects of parathyroid extract are well recognized. Perhaps local hyperoxia, in the form of increased vascularity, also plays a role in bone resorption in vivo. In this connection, it is noteworthy that extremely vascularized tissue has been found adjacent to the resorbing antlers of the deer prior to shedding.[11] Similarly, richly vascularized tissue has been described adjacent to resorbing deciduous teeth.[12]

In addition to the bearing which the above findings have on cellular remodeling of bone, the results obtained in this study indicate the potential value of introducing high concentrations of oxygen into other types of organ cultures. By inhibiting or slowing down massive cell death, which inevitably occurs within explants cultivated under relatively low oxygen tension, it appears possible to maintain or stimulate more optimal cell function in vitro.

It is anticipated that the use of hyperoxia for the routine production of bone resorption in tissue culture will provide a useful tool for further study of the origin, function, and fate of bone-resorbing cells and associated chemical changes. Furthermore, the finding of newly formed osteoid in the experimental cultures affords a *living* system for investigations concerning the mechanisms of bone formation and calcification.

Summary

The introduction of 95% O_2 and 5% CO_2 into the atmosphere of tissue cultures

of young mouse calvaria consistently resulted in rapid and marked bone resorption.

Time-lapse microcinematography and histological sections indicated active mobility and direct participation of macrophages, and probably of multinucleated osteoclasts, in the process of bone destruction.

Newly formed osteoid was found in many of the oxygenated cultures after the process of bone resorption had ceased.

It is suggested that this effect of hyperoxia may be similar to that of parathyroid hormone, both agents modifying the metabolic pathway of bone resorbing cells or their precursors and resulting in the local accumulation of substances required for bone resorption.

Mrs. Shirley Dolan provided technical assistance during this study.

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Thermal Gradients in Skin of Pigs and Rats During and Following Flash-Burns

Including Descriptions of Instrumentation and Procedure for the Quantitative Production of Flash Burn Exposures

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The clinical classification of thermal burns of the skin into first, second, and third degree is familiar. These groupings are dependent upon the evaluation, by gross inspection, of tissue changes in the skin present at some time following exposure to the skin to a damaging level of thermal energy. Thus, any antecedent physical or biological changes occurring to produce the burn by the absorption of thermal energy are represented only as an end-result of the thermal exposure. Further, the production of a burn of the skin is dynamically related to the physical properties of the source of the thermal energy as well as being dependent upon specific characteristics of the different layers of the skin.

Leach, Peters, and Rossiter [1] found that for external heat applications, with a specially designed heating iron, 50 C was a critical temperature in the production of irreversible damage to skin structures. In their search of the literature they reviewed the observations of Cohnheim (1873),[2] who temporarily stopped the circulation in the ears of rabbits with ligatures and then placed the ears in a water bath at an observed temperature. He found that immersions of 30 minutes in water at 45 C produced no effect. An immersion of 30 minutes at 49 C produced transient redness and swelling, and at all temperatures greater than 50 C severe damage was done. Similar results were reported by McMaster and Hudack [3,4] for the ears of mice.

Moritz [5] found that any elevation of tissue temperature of more than a few degrees above the level which is normal for the blood is potentially injurious. His experiments indicated that the higher the temperature to which tissue is raised, the lower the time required to produce a burn. Although certain temperature levels may be characterized as critical in respect to their capability of producing certain specific injurious effects, any elevation of tissue temperature above that which is normal for the blood in a homothermic organism may be critical in that it may produce injury if maintained for a long enough time.

Thus, it had been shown that skin was irreversibly damaged by even short exposures to temperatures exceeding 50 C. Simultaneously, closely allied skin structures were likewise damaged. This damage resulting from heat energy impinging upon the skin has been shown to be related to the calories per square centimeter per second of the heat source. In their extensive studies of thermal injury of the skin, Moritz [5] and Henriques [6] characterized the physical properties of various layers of the skin in relation to added calories required

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for the production of thermal damage. They showed that the production of a burn was dependent upon overcoming the existing thermal gradients of skin to cause the flow of heat into skin. Further, the alteration of these existing thermal gradients was dependent upon the heat capacity * and thermal conductivity † of the various layers of the skin. The following heat capacities were reported for pig skin in calories per gram per degree centigrade: epidermis, 0.86; dermis, 0.77; fat, 0.55, and muscle, 0.91. In addition, it was reported that the thermal conductivity of the layers of pig skin were as follows: epidermis, 0.03; dermis, 0.053; subcutaneous fat, 0.023, and underlying muscle, 0.066.

Thus, the heat capacity indicated that the various layers of skin differ in their ability to absorb heat. Similarly, the ability of the tissues of skin to conduct heat varied widely and partially defined some of the factors in the existing gradients that needed to be overcome in order to produce cutaneous burns. From these considerations, it was shown that the production of a cutaneous burn was a rate process, dependent upon the duration of the thermal exposure and the temperature attained. Thus, these factors determined the degree of damage produced. On the basis of these studies, it was suggested that an inverse relationship existed between the intensity of a thermal exposure and the time required to produce a burn.

Hogg, Payne, and Pearse[7] studied the effects of burns produced by exposure of skin for 0.35 second to the flash temperature of a magnesium bomb. Sheline, Alpen, Kuhl, and Ahokas[8] studied the burns produced by a 36 in. carbon-arc light operating at intensities between 2 and 67 cal. per square centimeter per second and exposure times from 0.1 to 8 seconds. Pearse and Kingsley[9] reported the time sequence of cutaneous thermal burns produced in pigs and dogs exposed to the flash of an atomic bomb. These animals showed that no burns were produced in the initial 25 milliseconds after the explosion. The severest burning occurred up to 0.5 second, and no burns occurred beyond 0.6 second after detonation of the bomb.

Thus, while these and other studies characterized physical conditions for the production of cutaneous burns, no data were available concerning thermal changes occurring in the skin during flash-burn exposure for the quantitative study of the dynamics of burn production. In the present report, therefore, instruments are described for the production of accurately calibrated flash-burn exposures and instruments for accurately recording intradermal temperatures at known depths below the skin surface during and following flash-burn exposure. From many experiments carried out during a period of three years, representative groups of these data are presented as thermal gradients in the skin of rats and Cheshire White pigs following flash exposure to a total of 5 cal.‡

In addition, the current report presents an effort to determine skin surface temperatures during flash-burn exposure in order to evaluate the effect of the skin surface as a barrier to heat under the known conditions described above.

Methods and Materials

Animals

In the early experiments, 175 to 250 gm. male rats of the Wistar strain were used. These animals were anesthetized by an intraperitoneal injection of 35 to 45 mg. of pentobarbital (Nembutal) per kilogram. The abdomen of the anesthetized rat was shaved clean preparatory to selection of the area to be burned. Suckling Cheshire White pigs, 4 to 6 weeks old, were anesthetized by the intravenous injection of 30 to 40 mg. of pentobarbital per kilogram. The abdomens of the anesthetized pigs

* Heat capacity is the amount of heat required to raise the temperature of a substance 1 C.

† Thermal conductivity is the ability of the skin to transport the heat applied.

‡ Dr. F. C. Henriques has calculated the temperatures expected at the subsurface sites given in the following studies with use of a mathematical method. These will be published separately at a later date.

were shaved clean in the areas selected for flash burning.

Description of Apparatus

Heat Source.—Radiant energy from a carbon-arc source operable between 15 and 100 amp. D. C. at 110 volts was focused by an aluminized SiO-coated elliptical mirror 25 cm. in diameter with conjugate foci of 11.9 and 41.25 cm. An area of uniform radiant flux of 4 sq. cm. was obtained at the burning plane by this ratio of focal lengths in combination with the size of the anode carrier. Both the mirror and arc were housed in an old-style Zeiss epidiascope. A square-wave heat pulse of radiant energy was obtained by means of a guillotine-type shutter (Fig. 1), located near the 41.25 cm. focal point of the mirror. When open, the aperture of this shutter was 1½ in. (3.8 cm.) square. Two aluminum plates (*P*), each 0.08 cm. thick, comprise the shutter, one being used for opening and the other, for closing. Each aluminum plate, mounted on drill-rod guides, was pulled upward by screen-door-type coil springs which exerted 18.8 kg. Sears constrain the aperture plates from moving until activated by solenoids in the circuit. Since the opening and closing time of the shutter are each 3.5×10^{-3} seconds (Fig. 2), the high mechanical energy levels thus generated necessitated the use of a damping mechanism to prevent self-destruction of the shutter device. The movable upper spring supports are hollow and are normally held down against the guide rods by the coil-spring tension. When each shutter was activated through the solenoids, the inertia of the spring and shutter forced the spring support to rise, thus forcing oil to flow downward through the capillary into the space above the guide rod. Critical damping was achieved through the proper choice of oil viscosity and capillary size in the guide rods of each shutter assembly.

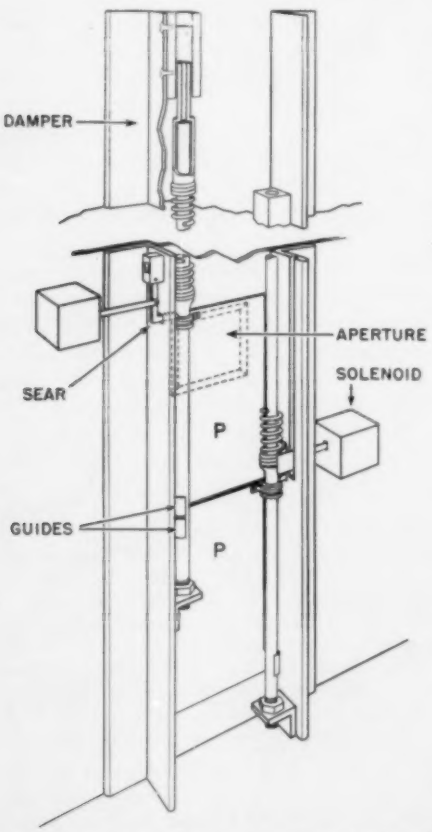


Fig. 1.—Guillotine shutter for the production of square-wave heat pulses.

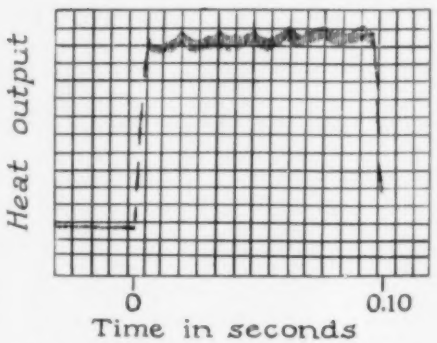


Fig. 2.—Shutter-speed test. Timing pulses, 1000 cps; ripple frequency, 60 cps.

In order to prevent the direct heat of the carbon arc from impinging on the thin aluminum shutter for more than 10 seconds during operation of the carbon arc, a solenoid-operated safety shutter of highly polished 0.3 cm. thick aluminum was interposed between the guillotine shutter and the carbon arc. This safety shutter automatically fell between the mirror and the plates of the guillotine shutter. The open time of the shutter was controlled by synchronously driven pin-cam timers adjustable between 0.1 and 10 seconds in 0.1 second increments. The various solenoids of the timer were actuated through microswitches which were operated by pins in a perforated timing disk.

Caloric Flux Measuring Equipment.—Total radiant flux ouput of the carbon arc was measured by a calorimeter in which the temperature rise of a stream of water pumped at a known rate was indicated by a thermopile connected to a galvanometer. Caloric flux from the carbon arc to the thermopile was absorbed by an acetylene-blackened

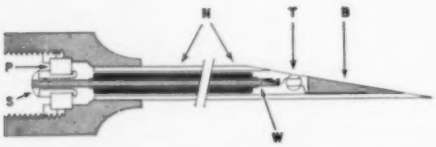


Fig. 3.—Hypodermic depth and temperature probe; thermistor needle. *B*, magnetic bit. *N*, JB No. 22 nonmagnetic stainless needle. *P*, Teflon. *S*, solder. *T*, Veco 32A5 thermistor. *W*, No. 30 SCC enameled copper wire.

silver disk, of 2 cm. square area, mounted in front of the thermopile. The calorimeter assembly was securely mounted at a known position parallel to and close to the front surface of the aluminum shutter plates (*P*) (Fig. 1) of the guillotine shutter. Thus, during calibration of the carbon arc, the shutter was opened and the caloric flux impinged on the calorimeter diaphragm in the identical position to be occupied later by the abdomen of animals being exposed to flash burning.

Calibration of the caloric flux of the carbon arc, with the calorimeter in place, was accomplished by devising a nomogram comparing the flow of water per second through the calorimeter with the galvanometer reading during exposure to the radiant flux of the carbon arc. The galvanometer reading in turn was interpreted in terms of calories per square centimeter per second delivered by the carbon arc.

Since the calorimeter could be used only during calibration of the carbon arc, a method was devised for monitoring the caloric flux output of the carbon arc on a continuous basis. The negative resistance of the carbon arc was found to correlate closely with the total radiant flux. A function of negative resistance was recorded on a meter simultaneously with the calorimeter described above during a calibration run of caloric output of the carbon arc. Thus, the caloric-flux output of the carbon arc was determined on an absolute basis by the water calorimeter and related to a secondary continuous recorder for periodic checks of the caloric flux, as needed, during flash-burning experiments.

Thermistor Probe Temperature Measurement.—In order to measure rapid temperature changes occurring at a given intradermal site during exposure of skin to a known caloric flux, a thermistor bead § was mounted in the tip of a 22 gauge 3.75 cm. nonmagnetic stainless steel hypodermic needle ‖ (Fig. 3). The thermistor bead (*T*) was embedded in epoxy resin curing agent Z ¶ so that its upper surface was tangent to the bevel of the needle tip. One platinum lead from the thermistor bead was swaged into a cotton-covered enameled copper wire and led coaxially in the channel of the hypodermic needle to an insulated terminal in the lock of the needle. The other platinum lead of the thermistor bead was soldered to the needle tip with pure lead (*S*). The water-immersion-thermal-time constant was determined by plunging the thermistor needle probe, at the room temperature of 20 C, into a water bath, the temperature of which was 40 C. The resultant rise in temperature attained by the thermistor was recorded on an oscilloscope screen. The oscilloscope tracing was photographed with use of a Polaroid Land Camera. A tracing of this photograph (Fig. 4) shows the water-immersion thermal time constant to be 10^{-1} seconds.

Adjacent to the position of the thermistor in the bevel of the 22-gauge hypodermic needle there was mounted also a ferromagnetic (*B*) bit, machined from soft iron and soldered into place with pure lead. After the bit was soldered, the bevel was carefully honed to a plane surface, with use of a hard Arkansas stone.

Since this iron bit was the only magnetic particle in the needle, its presence at a known position was used as a means of determining its location in relation to a recording circuit in the following manner. A penetron magnetic tape-erase head was placed in one limb of a balanced A. C. Wheatstone-bridge circuit. The tape-erase head was resonated by a shunt capacitance, the null condition being ascertained with use of the decibel scale of a

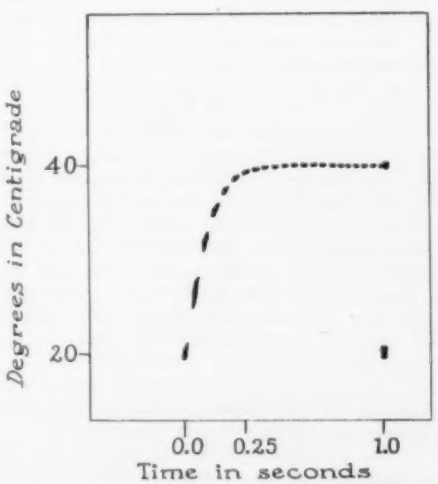


Fig. 4.—Temperature response of thermistor probe in water; 32A5 thermistor probe plunged into warm water. Temperature change recorded on oscilloscope and photographed. Trace, 20 spots per second.

§ Victory Engineering, Newark, N. J., Thermistor 32A5.

‖ J. Bishop Company.

¶ Shell Chemical Company, No. 828.

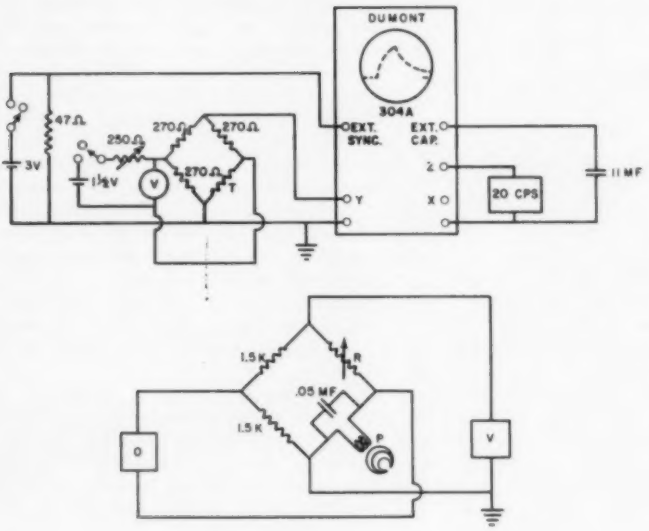


Fig. 5.—Electrical circuits for measurement of temperature alterations (top diagram) and depth of thermometer probe (bottom diagram). *O*, oscillator (Hewlett Packard 200 CD). *P*, Pentron tape-erase head. *R*, resistor (General Radio 1432 M). *V*, voltmeter (Ballentine No. 300). *T*, thermistor.

vacuum-tube voltmeter# (Fig. 5). Thus, with the Wheatstone bridge normally at balance nonmagnetic materials shunted across the gap in the erase head did not alter the balance of the bridge. However, ferromagnetic materials brought near the gap of the erase head unbalanced the bridge. The degree of this change in balance was read directly on the decibel scale of a voltmeter.

Since the dimensions of the ferromagnetic bit are small in comparison to the length of the gap of the erase head, the error recorded by the Wheatstone-bridge signal was a fairly simple inverse function of its distance from the gap of the erase head, for short distances.

Calibration of Hypodermic Depth Probe: Calibration of the hypodermic probe and tape-erase head combination in measuring distance was made by first balancing the Wheatstone bridge by successive adjustments of the bridge oscillator frequency (which was approximately 1 kc.) and voltage and the variable resistor arm until the voltmeter read 0 on the decibel scale. Decibel readings were then taken with the thermistor needle tip separated from the tape-erase head gap by layers of bond paper of known thickness. The resulting curve is nearly linear on semilog paper. A graph of decibel readings and their corresponding distance equivalents was then constructed.

In the experiments with rats and pigs being reported here, the depth of the hypodermic probe was determined by matching the decibel reading obtained with the predetermined micron value obtained in the calibration.

Ballentine 300 voltmeter.

Temperature calibration of the thermistor component of the hypodermic probe was carried out by immersion of the probe in a bath of Dow Corning Fluid 550 over a range of temperatures which varied from 25 C to 260 C. At 25 C the resistance of the 32A5 thermistor was 2000 ohms, while at 50 C the resistance was 260 ohms. With use of these values, the lined screen of the cathode ray oscilloscope was also calibrated for these temperatures in degrees centigrade for the purpose of following thermal changes at the site of the thermistor probe during flash-burning experiments.

Radiation Methods of Surface Temperature Measurements.—The instruments described thus far were used to measure thermal gradients in the subsurface areas of the skin during exposure to a known number of calories per square centimeter per second. As will be shown later, with the thermistor probe described, the shallowest depth at which thermal gradients could be measured was 80μ below the skin surface. Thus, since it was not possible to measure thermal gradients in the upper 80μ of the epidermis, an attempt was made to measure the skin surface temperature during exposure to a known caloric flux. Stoll[10] has described several methods for the measurement of skin surface temperature. Among these methods, a radiation method was the one of choice and was tried in conjunction with our studies of subsurface temperature.

A standard bolometer * with an arsenic trisulfide window was connected to a preamplifier † powered

* Servo Corporation of America, Type 1312.
† Servo Corporation of America, Model 1321.

by a power unit.‡ The bolometer was fitted with a polished aluminum cone to restrict its field of view to 7 degrees. The bolometer was mounted between the guillotine shutter (Fig. 1) and the abdomen of a pig (or rat) so that it viewed the portion being exposed to the caloric flux of the carbon arc during an experimental flash-burn exposure. Since it was noted that more heat was reflected than radiated from the skin of the animal being exposed to the known caloric flux, a time-sharing shutter, rotating at 32 rps was installed between the bolometer and the portion of the abdomen of the animal being exposed. This shutter permitted heating of the exposed skin surface to flash burning for 60% and permitted measuring of temperature of the exposed skin site by the bolometer for 20% of the cycle. Under these conditions, the bolometer output, indicated on the screen of a cathode-ray oscilloscope, was 0 without a test animal in the fixed flash exposure position. Calibration of the bolometer was done by exposing an acetylene blackened cone previously heated to a known temperature in the exposure position to be used for the experimental animals (pigs). The bolometer and oscilloscope were A. C.-coupled, since the heat signal was a series of pulses produced by the time-sharing shutter. The time-sharing shutter had three openings for heating and three openings for the measurement of heat. At a rotational speed of 32 rps the pulse frequency was 96 per second. The heating of the bolometer during this cycle was recorded on the screen of the oscilloscope. These recordings gave the heat measurements of the bolometer as an alternating band of variable width. The peak temperature attained by the bolometer was represented by the widest portion of the tracing.

Skin Clamp for Immobilizing Test Areas of Abdominal Skin Prior to Flash Burn Exposure.—A preselected area of the skin of a pig (or rat) was held rigidly in place by a skin clamp (Fig. 6). By means of this clamp the desired area of skin was stretched between two rows of steel phonograph needles mounted at opposite sides of an aluminum rectangle. One row of needles was fixed in the frame of the holder. The opposite set of phonograph needles was seated in a movable plunger controlled by a spring. The immovable row of needles was seated in the abdominal skin. The intervening region of skin was stretched taut to a controlled degree by the release of the plunger portion of the aluminum frame that contained phonograph needles, the points of which were directed in the opposite direction to those seated in the fixed side of the frame. The animal, a portion of whose abdominal skin was thus immobilized, was rigidly held between two adjustable aluminum plates mounted on a movable table, to permit movement of the animal fixed to the table without altering the position of the skin clamp. In addition, the movable table contained a jig for directing the thermistor probe into the subsurface of the skin at a fixed angle within the rectangular area immobilized by the clamp. This jig also served as a lock to hold the thermistor probe rigidly in position after its insertion subdermally. This entire assembly was positioned rigidly at an appropriate position in front of the guillotine shutter and in relation to the focal point of the mirror focusing the carbon arc before each flash exposure.

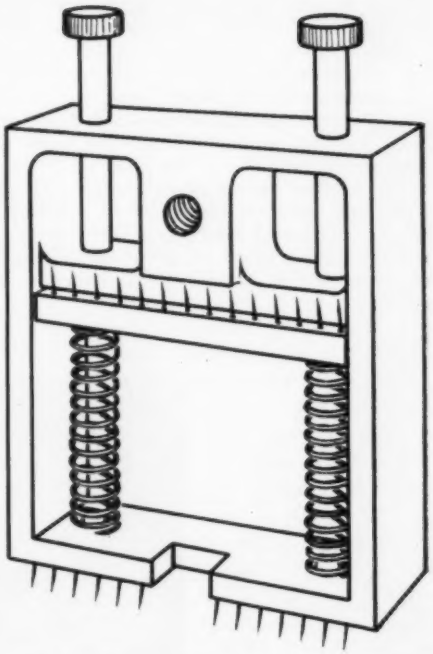


Fig. 6.—Skin-stretcher clamp for immobilizing test areas of skin.

During flash-burn exposure the thermal events in the skin were recorded on the screen of a cathode-ray oscilloscope, and this image was photographed by an attached Polaroid Land Camera.

Sequential Procedures in Determination of Depth Measurements and Thermal Gradients with Use of Hypodermic Probe During Flash-Burn Exposure

1. The animal was anesthetized by the injection of pentobarbital.

2. The abdomen was shaved clean with use of soap and water. The shaved area was then thoroughly dried to avoid the presence of any water

‡ Servo Corporation of America, Model 1330.

film on the skin surface that might interfere with the transfer of thermal energy in the subsequent flash-burn exposure.

3. A selected area of the skin of the abdomen was immobilized with the skin clamp.

4. The hypodermic probe was inserted into the skin. The butt of the needle was then locked in place in the frame of the skin clamp.

5. The animal and the skin clamp, carrying the hypodermic probe, were secured to a common frame, thus assuring immobility of both the animal and the probe as well as permitting their safe movement to the platform of the flash-burning machine.

6. Readings of depth measurements were made in duplicate, and the voltmeter readings and their corresponding depth equivalents, recorded.

7. The immobilized animal with the hypodermic probe in situ was transferred to a predetermined position in front of the guillotine shutter of the carbon-arc flash-burning machine and in the focal plane of the mirror in the carbon-arc machine.

8. The caloric flux of the carbon arc had been previously standardized. Flash burning of the area of skin in which the hypodermic probe was immobilized was promptly carried out by activating the guillotine shutter. Thus, without disturbing the location or angle of insertion of the probe,

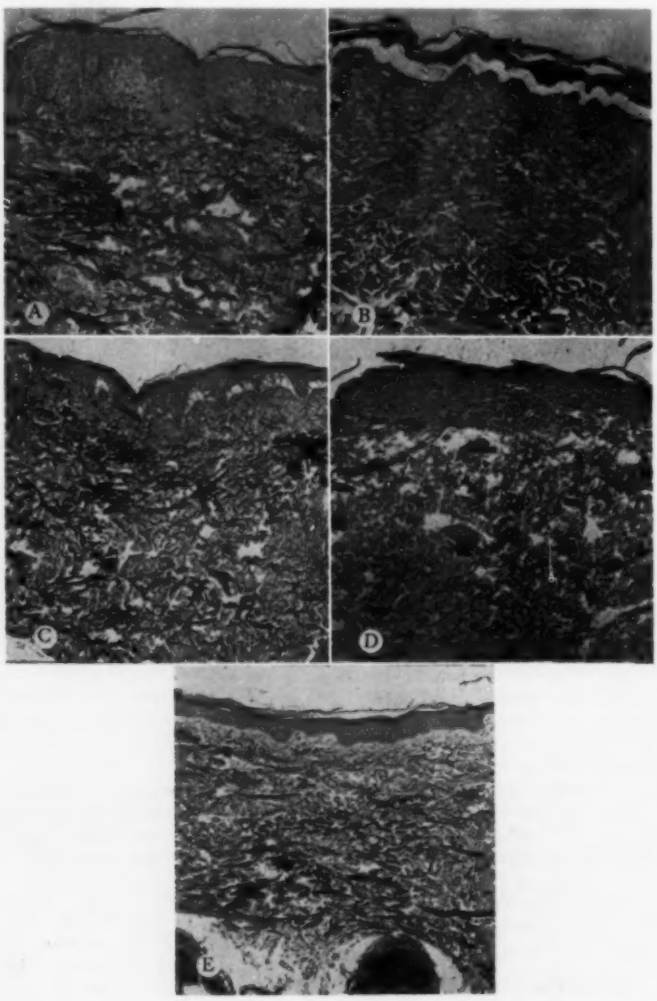


Fig. 7. — Hematoxylin-and-eosin-stained sections of skin from the abdomen of the Cheshire White pig, excised immediately after thermal exposure of known caloric flux and length of exposure. (*a*) After exposure to 5 cal. per square centimeter per second for one second (unpainted with India ink). (*b*) After exposure to 10 cal. per square centimeter per second for 0.5 second (unpainted with India ink). (*c*) After exposure to 5 cal. per square centimeter per second for 1.0 second (painted with India ink). (*d*) After exposure to 10 cal. per square centimeter per second for 0.5 second (painted with India ink). (*e*) After exposure to 5 cal. per square centimeter per second for 0.3 second (painted with India ink).

thermal exposure was obtained. The image transmitted to the cathode-ray oscilloscope was photographed. In the data being presented, the combination of caloric flux per square centimeter per second and length of the exposure was always arranged to give a total of 5 cal.

Since the physical methods described permitted the precise determination of temperatures at known depths in the skin following thermal exposures of known caloric flux, it appeared of value to supplement these studies with histological studies of skin under these conditions. Thus, immediately following the thermal exposure of the skin of the abdomen of pigs, blocks of the exposed skin were fixed in formalin. Routine hematoxylin-and-eosin-stained sections of pig skin were prepared following exposure to 5 cal. per square centimeter per second for 1 second and 10 cal. per square centimeter per second for 0.5 second.

In addition, in conjunction with the determinations of "surface" temperature measurements previously described, routine hematoxylin-and-eosin-stained sections were also prepared of pig skin which had been painted with India ink before the thermal exposure. Pig skin painted with India ink was exposed to flash exposure of 10 cal. per square centimeter per second for 1.0 second and 5 cal. per square centimeter per second for 1.0 and 0.2 second. Photomicrographs of representative burned areas of pig skin are presented (Fig. 7). In addition, the depth of altered collagen calculated from the hematoxylin-and-eosin-stained sections in each case was measured by means of an ocular micrometer.

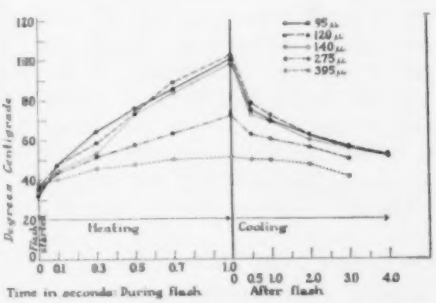
Results

Thermal Gradients in Skin of Cheshire White Pigs During and After Flash-Burn Exposure to Total Five Calories.—From early experiments it was apparent that the device of a hypodermic probe containing elements for recording the depth of the thermistor and the subsequent temperature changes in its immediate environment was a feasible method for determining thermal gradients in the skin. However, to assure the accuracy and reproducibility of these results in relation to each other for a given caloric flux, the carbon arc was monitored continuously by measuring its negative resistance. Similarly, both the portion of abdomen of the animal to be flash burned and the hypodermic probe were immobilized to assure valid comparisons between a given depth measurement and the subsequent thermal changes occurring at the thermistor site during and after flash-burn exposure. Thus, at all stages of a single determination of depth and temperature changes, control and monitoring devices were arranged to approach a degree of reproducibility and accuracy necessary to validate the subsequent findings.

TABLE 1.—*Flash Burns of Skin in Cheshire White Pigs and White Rats with Use of a Total of Five Calories*

	Thermal Exposure		Ranges Measured	
Animal or Specimen	Cal/Cm²/Sec.	Seconds	Depth, μ	Temperature, C
Pig, anesthetized	5.0	1.0	95-395	101-51
Pig Skin excised from abdomen	5.0	1.0	110-330	105-63
	10.0	0.5	95-560	116-68
	16.3	0.3	125-555	118-78
Rat, anesthetized	5.0	1.0	95-275	96-75
	9.8	0.5	80-465	116-68

Over much of a three-year period during which these controls were being devised, white rats were used in the experiments. Subsequently, for the final data, Cheshire White pigs were used as well as white rats. Thermal gradients in the skin of both animals exposed to a total of 5 cal. were determined. Exposure to a flash burn of a total of 5 cal. was obtained by varying the caloric flux between 5 and 16.3 cal. per square centimeter per second and appropriately adjusting exposure times from 1.0 second to 0.3 second (Table 1). Thermal gradients were obtained at subsurface sites in the skin of rats and pigs which ranged from 80μ to 560μ.



Graph 1.—Thermal gradients in anesthetized pig exposed to 5 cal. per square centimeter per second for 1.0 second.

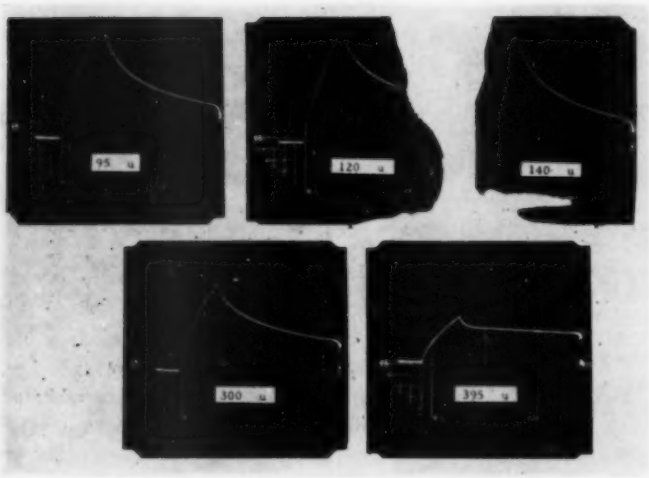
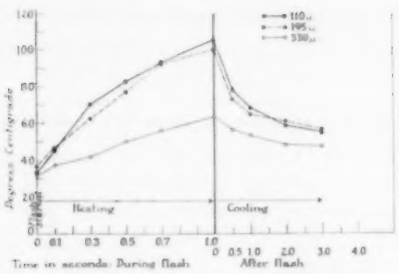


Fig. 8.—Thermal gradients in pig skin at 5 cal. per square centimeter per second.

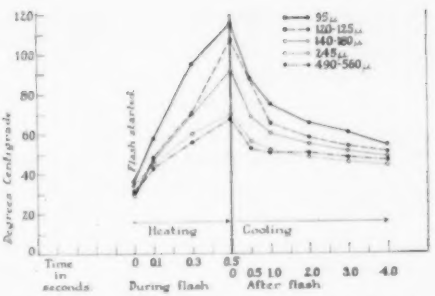
After exposure of skin of the abdomen of the pig to 5 cal. per square centimeter for one second (Graph 1) the highest temperature obtained at 95μ beneath the skin surface was 101 C (Graph 5). In the rat, at 95μ the temperature was 96 C, and in excised pig skin the highest temperature was 105 C at 110μ beneath the skin surface. The temperatures recorded at the deepest dermal site measured after exposure to 5 cal. per square centimeter per second for 1 second were 51 C at 395μ in the pig, 75 C at 275μ in the rat, and 63 C at 330μ in excised skin of the pig. After exposure to 10 cal. per square centimeter per second for 0.5 second the highest temperatures recorded were 116 C at 95μ in excised pig skin and 116 C at 80μ in the rat. The lowest temperatures recorded after 10 cal. per square centimeter per second for 0.5 second were 68 C at 560μ in excised pig skin and 68 C at 465μ in the rat. After 16.3 cal. per square centimeter per second for 0.3 second the highest temperature recorded in excised pig skin was 118 C at 125μ, while the lowest temperature was 78 C at 555μ.

The values for all the ranges given in Table 1 were obtained by measurement from actual photographs of the cathode-oscilloscope image of thermal events at the thermistor site during and after thermal exposure. In an actual set of photographs presented (Fig. 8), the thermal gradients recorded at 95μ, 120μ, 140μ, 300μ, and 395μ beneath the skin surface during the exposure to 5 cal. per square centimeter per second for 1.0 second are reproduced. In each photograph the straight horizontal portion of the tracing at the extreme left shows the initial temperature of the thermistor site before flash burning. The sharp upward rise represents onset of flash burning without correction for the 0.10 second time-constant correction required to establish thermal equilibrium between the thermistor and its immediate environment. The peak of each tracing shows the highest temperature attained at the depth marked on each record. The guillotine shutter automatically closed at this point, and therefore the descending limb of each record shows a cooling curve at the specific depth site of the probe with which each record is labeled. At the extreme right of each record a dot is present representing a temperature-calibration check of the oscilloscope screen.

From similarly obtained photographs the thermal gradients during and after flash-burn exposure to a total of 5 Cal. were plotted as composites for skin of the anesthetized rat in which 9.8 cal. per square



Graph 2.—Thermal gradients in pig skin exposed to 5 cal. per square centimeter per second for one second.



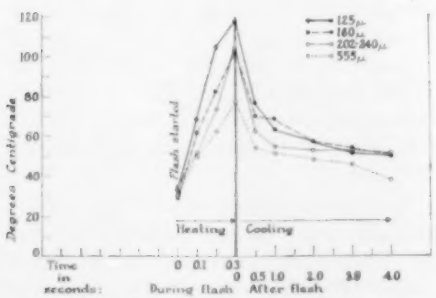
Graph 3.—Thermal gradients in excised pig skin exposed to 10 cal. per square centimeter per second for 0.5 second.

centimeter per second for 0.5 second and 5.0 cal. per square centimeter per second for 1.0 second were used. Similarly, a composite was made of a 5 cal. flash burn (Graph 2) of the skin of the anesthetized Cheshire White pig after exposure to 5 cal. per square centimeter per second for 1.0 second. And finally Graphs 3, 4, and 5 composites are presented of 5.0 cal. flash-burn exposure of excised pig skin to 5 cal. per square centimeter per second for 1.0 second, 10 cal. per square centimeter per second for 0.5 second, and 16.3 cal. per square centimeter per second for 0.3 second. These data represent many trials obtained on different days and different animals. The depth and temperature values in many instances given represent averages of several experiments.

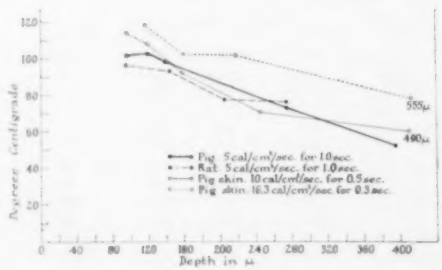
These data showed that the skin of the anesthetized rat and pig as well as the excised skin of the pig respond essentially similarly to a given thermal exposure. In the subsequent discussion and illustrations, only the data obtained on pig skin are presented. Thus, at depths up to approximately 200μ beneath the surface of the skin a relatively straight-line relation existed between depth and temperature attained. At depths deeper than 200μ the rate of temperature rise was less rapid than at shallow sites.

The cooling curves, after all the flash-burn exposures, showed rapid decay and within 4.0 seconds after all the burns subepidermal temperature had returned to 54 C or less irrespective of the peak temperature attained or the caloric flux used in producing the burn.

These data were also transposed to give the rates at which subepidermal temperatures rose and the rates at which cooling occurred (Table 3) after flash-burn exposure to a total of 5 cal. Inspection of these data shows temperature increases that vary in relation to the depth beneath the surface at which the



Graph 4.—Thermal gradients in pig skin exposed to 16.3 cal. per square centimeter per second for 0.3 second.



Graph 5.—Peak temperatures attained in rat and pig skin exposed to a total of 5 cal. by flash burn.

TABLE 2.—*Thermal Gradients in the Skin of Cheshire White Pigs During and After Flash-Burn Exposure to Five Calories*

Animal of Specimen	Caloric Flux Rate Cal/Cm²/Sec.	Duration of Exposure, Seconds	Depth of Measurement, μ	Temperature Gradients * During Flash (Heating), Sec. 0.1	0.3	0.5	0.7	1.0	After Flash (Cooling), Sec. 0.5	1.0	2.0	3.0	4.0
Excised pig skin	5.0	1.0	110	45 †	70	82	92	105	77	68	59	55	
			195	46	62	77	87	100	73	69	60	56	
			330	37	41	50	56	63	56	52	48	47	
	10.0	0.5	95	58 ‡	95	116	—	—	88	75	65	60	54
			120	48	70	108	—	—	88	68	57	53	51
			140-180	49	70	92	—	—	69	61	55	51	48
			245	47	60	70	—	—	57	52	49	46	44
			490-560	44	56	68	—	—	53	52	50	48	46
	16.3	0.3	125	68 §	118	—	—	—	70	69	57	53	51
			160	61	102	—	—	—	62	63	56	52	50
			205	57	104	—	—	—	67	64	54	51	50
			220-240	50	105	—	—	—	67	68	55	53	52
			555	50	78	—	—	—	54	51	48	46	38
Anesthetized pig	5.0	1.0	95	47 ‖	64	75	85	101	75	70	62	57	
			120	47	58	74	89	102	79	72	62	57	
			140	44	53	73	83	99	74	70	60	56	52
			275	43	51	57	63	72	63	60	56	50	
			395	40	45	47	50	51	50	50	50	48	41

* In degrees centigrade.
† Average body temperature before flash exposure, 33 C.
‡ Average body temperature before flash exposure, 31 C.
§ Average body temperature before flash exposure, 34 C.
‖ Average body temperature before flash exposure, 35 C.

hypodermic probe was located. It was noted that the largest increment of temperature rise occurred within the first 0.3 second after onset of flash exposure at shallow depths. Thus, thermal changes at 110μ during exposure of pig skin to 5 cal. per square centimeter per second for 1 second revealed that a total rise of 37 C occurred between 0 and 0.3 second, while only a 35 C rise occurred in the remaining 0.7 second of exposure. At deeper levels in pig skin, temperature increments were relatively constant throughout the exposure, with some tendency to rise in the last 0.5 second of a 1.0 second flash exposure to 5 cal. per square centimeter per second.

TABLE 3.—*Skin Surface Temperatures of Cheshire White Pigs Flash-Burn Exposure*

Skin Surface	Caloric Flux Rate, Cal/Cm.²	Exposure Time, Seconds	Total Cal.	Surface Temperature (Bolometric Method), C
Not painted	2.8	2.0	5.6	60
	3.9	1.0	3.9	56
	4.5	1.0	4.5	60
	5.0	1.0	5.0	86 *
	5.0	2.0	10.0	100
	8.5	0.6	5.1	96
Painted with India ink	5.0	1.0	5.0	400+ *
	5.0	0.5	2.5	133
	5.0	0.3	1.5	110

* Average intradermal temperature obtained by thermometer probe after 5 cal/cm²/sec. for 1 second is 85 C.

In contrast, during exposure flash burns of high caloric flux the temperature increments were rapidly rising at all depths measured throughout the exposure. Thus, during exposure to 16.3 cal. per square centimeter per second the temperature increments rose during the first 0.1 second of exposure 16 C and 27 C, respectively, for depths between 125μ and 555μ. In contrast, the temperature increments between 0.1 and 0.3 second for the same depths were between 27 C and 55 C.

Histological examination of pig skin immediately after thermal exposure to 5 cal. per square centimeter per second for 1 second (Fig. 7*A*) revealed the presence of marked damage that extended transepidermally and showed loosening at the epi-

dermal-dermal junction. In addition, there was fragmentation and damage of the superficial collagen to a depth of approximately 150μ beneath the epidermal surface. After exposure to 10 cal. per square centimeter per second for 0.5 second (Fig. 7*B*), the hematoxylin-and-eosin-stained sections showed transepidermal destruction and homogenization and destruction of the dermal structures which extended to approximately 480μ beneath the epidermal surface.

When the epidermal surface was coated with India ink, thermal exposure to 5 cal. per square centimeter per second for 1 second (Fig. 7*C*) resulted in loosening of the epidermal-dermal junction with minimal change in the epidermis or underlying collagen of the dermis that extended 90μ into the upper dermis. When the pig skin was painted with India ink and exposed to 10 cal. per square centimeter per second for 0.5 second (Fig. 7*D*), there was transepidermal necrosis and homogenization of the upper dermis for a depth of approximately 175μ. When the caloric flux was reduced to 5 cal. per square centimeter per second for 0.3 second (Fig. 7*E*), there was minimal evidence of damage to the epidermis or underlying dermis. Questionable damage to the collagen measured 35μ.

Comment

It has been stated previously that an inverse relationship existed between the intensity of a thermal exposure and the amount of time required to produce a burn. Also, it has been established that the elevation of the temperature of skin to 50 C or more for even short periods of time resulted in the production of irreversible damage to collagen and epidermis of the skin. However, the rate and sites at which these damaging changes occurred during and after a given thermal exposure of known calories per square centimeter per second and time of exposure have not been available previously. In the present studies, use of the quantitative instrumentation described permitted analysis of thermal events occurring in the skin as a result of flash burning and their interpretation.

When the total caloric flux of a thermal exposure was held constant at 5 cal. by varying the time of thermal exposure proportionate to the caloric flux rate, the peak temperatures at any given site in the subsurface of the skin was always higher when the rate of caloric flux was increased. Thus, during exposure of the skin of rats and pigs to 5 cal. per square centimeter per second for 1.0 second, the peak temperature at 95μ below the skin surface was between 95 C and 101 C, while thermal exposure to 10 cal. per square centimeter per second for 0.5 second resulted in a peak temperature of 116 C at 95μ below the skin surface of the pig and 118 C at 80μ in the rat. Comparable differences in the peak temperatures reached were also found at deep sites in the subsurface of the skin. After 5 cal. per square centimeter per second for 1.0 second, the peak temperature at a depth of 395μ in the pig was 51 C, while after 16.3 cal. per square centimeter per second for 0.3 second, the peak temperature at 555μ was 78 C.

Inspection of the peak temperatures attained at a number of subsurface sites during thermal bombardment of the skin surface to a total of 5 cal. deliverd at three different rates suggested an inverse relationship between the temperature rise and the caloric flux used. From photomicrographs of actual burns, the temperature increments at selected times after the onset of thermal exposure were determined. During the exposure to 5 cal. per square centimeter per second for 1.0 second, successive temperature increments at shallow depths below the skin surface (e. g., up to 195μ) showed a peak temperature increment at approximately 0.3 second after onset of the flash exposure and relatively smaller increments in temperature both before and after 0.3 second of the exposure. In contrast, thermal exposure to caloric bombardment of greater intensity (e. g., 10 cal. per square centimeter per second for 0.5 second or 16.3 cal. per square centimeter per second for 0.3 second),

yielded temperature increments that increased continuously or were maintained at high levels throughout the thermal exposure. In addition, at deeper sites (e. g., 200μ or more) in the subsurface of the skin during exposure to 5 cal. per square centimeter per second for 1.0 second, temperature increments of almost constant amounts were found throughout the thermal exposure. As the rate of caloric bombardment was increased, the temperature increments at deeper sites tended to increase with time during flash-burn exposure. In addition, these sites were also at higher temperature levels throughout the exposure than the temperatures reached at a lower rate of delivery despite a final total of 5 cal. being delivered in all cases. Thus, these observations, representing the flow of heat into the skin during thermal bombardment, yielded a series of patterns in which the temperatures reached were generally inversely related to length of exposure. In addition, the final temperatures probably were related, in part at least, to the differences in heat capacities and conductivities present at different sites in the tissues of skin. The effectiveness of the relatively greater heat capacity of epidermis (0.86 cal. per gram per degree centigrade) might account, in part at least, for the marked difference in the pattern of heat flow into these areas in the initial milliseconds of thermal exposure.

In contrast, the heat flow during later stages of the thermal exposure was more constant, especially at deeper sites in the skin. This probably represented saturation, by thermal energy, permitting steady flow of heat through these areas. Since the thermal gradients determined in the present studies were those occurring only in the immediate enviroment of the single hypodermic probe, thermal changes during flash exposure in the perimeters of this focus were not known. The flow of heat into this perimeter of tissue was occurring both from the surface and from adjacent deep tissues during flash exposures. Hence, if the temperature elevations in the areas away from the site of the hypodermic probe were elevated to 50 C or more, additional irreversible burn damage might be expected at these sites. The validity of this possibility could be checked by the placing of additional hypodermic probes at sites away from the center of the site of flash burning. In other studies involving the histochemical recognition of thermal injury to collagen [11] by special staining methods, irregular collagen damage was frequently seen in the margins of circumscribed flash burns. These areas subsequently had the gross and microscopic appearance of burn injury and perhaps represented areas of the entity referred to as "latent burn injury."

After the termination of flash burns at the three-intensity studies, cooling of skin structures occurred rapidly at all levels. Indeed, there appeared to be only a minor relationship between the conditions of burning and the time required for all levels to cool to the range of 50 C or less. Thus, the damage produced by exposure to flash burns of the magnitude described in the present report would appear to begin within the first 0.1 second to 0.3 second of onset of the exposure and continue until the exposure was over. By 4.0 seconds after the flash exposure has passed the central areas of the area exposed to a given caloric flux had cooled to the range of 50 C to 54 C.

The presence and extent of damage found in the histological preparation of pig skin excised immediately after flash burning corresponded well with the physical data collected on actual temperatures attained during the flash-burn exposures. In the areas in which temperatures had been elevated above 50 C by burning, irreversible damage was noted in epidermis and dermis. The higher rate of delivery of caloric flux (10 cal. per square centimeter per second) produced damage of greater degree and to greater depths than did exposures to a lower caloric rate (5 cal. per square centimeter per second) despite the fact that a total of 5 cal. was used in both instances.

The bolometric infrared reflection method for the determination of skin surface temperatures yielded results that were incom-

patible with the subsurface temperatures found with use of the thermistor probe during caloric bombardment of pig skin. In all instances, the maximum temperatures recorded by the bolometric method gave skin temperatures which were lower than the shallow subsurface temperatures measured by the thermistor. The surface temperatures were also higher than the deepest subsurface temperatures. It was found by inspection that the surface temperature being measured corresponded best with a mathematical average of the total of the subsurface temperatures attained during exposure to any given caloric rate and time of exposure. Thus, the surface temperature during exposure to 5 cal. per square centimeter per second for 1.0 second was 86 C. The average of the subsurface temperatures under the same conditions was almost identical (85 C). Since the bolometric method is dependent upon infrared radiation, it became apparent that the skin was transparent to infrared and thus the temperatures recorded were an average of temperatures that had occurred in the full thickness of skin rather than on its surface.

The observations of skin temperatures in which the skin was first coated with India ink added further confirmation to this observation. Since India ink is almost totally opaque, nearly all the radiant energy impinging on this surface is absorbed by the India-ink layer. Thus, it was noted that relatively minor injury occurred to the underlying skin in the presence of temperatures up to 400 C as compared to thermal exposure of uncoated pig skin to comparable caloric flux.

Summary

Instrumentation was described for the determination of thermal gradients in the skin of pigs and rats during and following thermal exposure to known caloric flux and time of exposure. In general, it was shown that there was an inverse relationship between the temperature attained in the skin and the radiant energy of the exposure used. However, it was shown that as the caloric rate was increased, higher temperatures were obtained in the skin despite a constant exposure with respect to total calories.

The infrared reflection method was shown to measure an average of full-thickness temperatures in the skin during flash-burn exposure rather than skin surface temperatures. Thus, no measurements of skin surface temperature were possible under the conditions described.

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Some Considerations Concerning the Nature of the So-Called Sarcoma of Kaposi

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The morphologic unit of the disease process currently referred to as Kaposi's sarcoma consists of a complex growth of vascular channels and mesenchymal cells of various types and in different phases of differentiation. Although eponyms are not very desirable, they become a necessity in a condition such as the one under consideration in which the cause is unknown and in which there is great variation in histologic pattern and in clinical course. Regardless of the uncertainties that still exist concerning the nature of the process, one fact seems clear, namely that Kaposi's sarcoma is somehow related on one hand to the proliferative disorders of the reticuloendothelial system and on the other hand to the angioblastic group of neoplasms. Consideration of the nature of these relationships and their histogenetic significance is the main purpose of the present study.

1. Epidemiologic Considerations

Over 600 cases reported from the time of Kaposi's original description (1872)[76] indicate that the disease encompasses a wide range of clinical and pathological manifestations, heavily influenced by geographical, racial, and sex-linked characteristics, which factors, although they undoubtedly possess fundamental significance, thus far serve only to obscure further the understanding of the nature of the condition.

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As noted throughout the literature, the peak incidence of the disease is between the fourth and the seventh decades of life,[130] but cases have been reported in children,[32] adolescents,[68,78,83,130] and in a 6-month-old infant.[22] Not infrequently the earliest manifestations of the disease can be traced back to when the patient was still young, followed by the typical signs and symptoms later in life.

The predominance of this condition in people of Jewish and Italian extraction has been commented upon by several investigators,[83] but it is not clear if this predominance stands on a geographical or a racial basis. Of the 356 cases reviewed by Dörffel,[34] 111 were Italians; 50, Russians; 20, Poles, and 45, Jews. The remainder of the cases represented various nationalities, including Australians, Americans, Hungarians, and Germans. In Azulay's series[4] from Brazil there was not a single Jew, and the same is true of De Amicis' 50 cases. In Ronchese and Kern's series[112] of 16 cases, 10 of the patients had been born in Italy; 3, in Russia, and 1 each in the United States, England, and Lithuania. There were only four Jews in the series, one born in the United States and three of Russian origin. As Dörffel[34] says, it is more likely that the distribution of the disease is geographical than racial, but the significance of this is not clear. It is possible that the apparently higher incidence of the disease in Central Europe may be related to factors of recognition and that with increased world-wide awareness of its existence present statistical data might be considerably altered. Bluefarb[16] does not hesitate to state that the old concept that the disease is lim-

ited almost exclusively to Jews is erroneous and that there is no proof that the race of the patient is an etiological factor in this disease.

Another point that needs to be reconsidered is the often-repeated statement that Kaposi's sarcoma is far more frequent in people of the white race than in the Negro. This contention was well justified by the fact that prior to the study of Dupont et al.[35] (1949) only 10 instances of the disease had been recorded in Negroes.[38,73,98,102] However, since then, a number of additional cases have been reported from the Belgian Congo,[36,111] 1 case has been added by Syrop and Krantz,[127] and 33 were found in the files of the South African Institute for Medical Research between 1942 and 1949.[75] Three additional cases were disclosed by Hazen and Freeman [67] among 129 cutaneous malignancies in Negro patients, and these investigators do not hesitate to express the opinion that Kaposi's sarcoma is found as frequently in the Negroes as in the people of the white race. According to Findlay,[42] the incidence of Kaposi's sarcoma in West Africa is at least 1 case in 50,000 among the young adult population.

To my knowledge, only two cases of Kaposi's sarcoma have been reported in Orientals, a 16-year-old Chinese boy who developed the disease at 8 years of age [78] and the case of a Japanese woman.[40] Banerjee [6] has described a case in a Hindu.

Unchallenged remains the notion that Kaposi's sarcoma occurs more frequently in the male than in the female. Among the 356 cases analyzed by Dörffel,[34] in 1932, there were 325 men and 21 women, a ratio of 15:1. The same trend is shown by the survey of 434 cases by Choisser and Ramsey [23] (1939), which includes only 5.99% females. From that date to 1950, Bluefarb [16] found 144 additional cases in which the sex was given, among which there were only 15 women, or 9.6% of the total. A comparable sex distribution is shown by Ronchese and Kern [112] in a subsequent series of 16 cases (1953), including 15 males and a single woman.

The fact that the disease is rare in women leads to the consideration of possible endocrine factors. Hurlbut and Lincoln [72] have advocated the rationale of treating Kaposi's sarcoma with estrogenic hormones, and they mention the case of a patient (Case 2) who showed some improvement with the onset of spontaneous feminizing changes. The possible role of endocrine imbalance is further indicated by the apparently notinfrequent coincidence of Kaposi's sarcoma and diabetes mellitus, an association that the same investigators found in 6 of 13 cases they studied.

Along these lines it is pertinent to recall an experiment of Andervont and Dunn,[2] showing that female mice are far more susceptible than the males to induction of angiomatous tumors by *o*-aminoazotoluene and that the incidence of tumor occurrence can be markedly reduced by castration or by implantation of testosterone pellets.

Kaposi's sarcoma has been said to be more frequent among laborers and outdoor workers than among office employees and professional men. According to Van Cleve and Hellwig,[131] approximately 95% of the reported cases are found among laborers and a scant 5% among white-collar workers. In McCarthy and Pack's series,[83] in which this point was investigated, the occupations of the patients were too diversified to support this common belief. However, these authors did note among their patients a prevalence of occupations which required the person to be on his feet for long periods of time. When the manifestations of the disease are grouped according to anatomical distribution, it becomes apparent that legs and arms, including hands and feet, often bilaterally and in a symmetrical fashion, are the most frequent sites of primary involvement. It seems possible that a relation exists between the positional habits of the patient with Kaposi's disease and the anatomical distribution of the lesions and that

the link between the two may possibly be found in lymphedema.

Swelling of the extremities, usually symmetric in distribution, is in fact one of the commonest early manifestations of the disease.[30] Since lymphedema can predispose to the development of angioblastic malignancies,[123] it is not unreasonable to entertain the thought that some relation may intercede between the standing habits, the ensuing peripheral edema, and the anatomical distribution of the Kaposi's lesions. Significant in this respect are a case of Aegerter and Peale[1] and another of Hansson[66] in women who developed Kaposi's sarcoma of the lower extremities, 9 and 29 years, respectively, after the onset of massive lymphedema following an infection.

A study by Pack[96] indicates that patients with Kaposi's sarcoma frequently exhibit flat feet, short sturdy legs, thick ankles, tight inelastic skin, and varicosities, all of which may be considered factors predisposing to circulatory disturbances of lower extremities and consequently to lymphedema.

2. Etiology

In the present state of knowledge there are very few hints as to the cause of the process. Some classify Kaposi's sarcoma among the neoplasms, and some others, among the granulomas. The latter view is based upon the histologic appearance of the lesion in some stages in the process and upon the assumption that the disease is due to an infectious agent.

Greco et al.[54,56] isolated a fungus from several members of the same family, all clinically affected by Kaposi's disease, and they named the organism Cryptococcus haematicon. Other investigators have been unable to confirm this finding. Dillard and Weidman[33] found a fungus resembling Trichophyton schoenleini in mesenteric and gastrohepatic lymph nodes from a case of the same disease, but the possibility of secondary parasitic invasion cannot be excluded. Furthermore, several attempts to reproduce the lesion by homologous and heterologous tissue transplants[24,90,95] have failed. The only claim of successful transplantation is that of Justus,[74] who described collections of mesenchymal cells, especially around the arteries in the lungs, heart, and liver of a white mouse into which an emulsion of rapidly growing Kaposi sarcoma had been injected subcutaneously. He further succeeded in reproducing a comparable mesenchymal-cell reaction in five generations of mice given inoculations of an emulsion of kidney of the animal originally given the injection. However, it should be remembered that a proliferation of mesenchymal cells, particularly those located in proximity to the walls of blood vessels, is a common nonspecific response to the parenteral introduction of foreign proteins.

Inoculation into the anterior chamber of the eye of the guinea pig of tissue from a Kaposi lesion has yielded negative results.[39,116] Despite conflicting evidence and with the reservation that the entity now designated "Kaposi's sarcoma" may in actuality be two different conditions (namely, granuloma and sarcoma) with some manifestations in common, the present trend favors the concept that the disease is caused by some systemic carcinogen which acts upon the mesenchymal tissue. In favor of this hypothesis is the demonstration by Andervont, White, and Stewart[3] that lesions resembling those of Kaposi's sarcoma can be induced in animals by injections of chemical carcinogens.

Various writers have speculated on the relative roles of predisposing causes and exciting factors, such as trauma, exposure to cold, and therapeutic administration of arsenic, to explain the initiation of the process and the subsequent transformation of an apparently benign granulomatous process to an obviously malignant lesion.[16,24]

3. Histogenesis

Emphasis in several publications[23,34,130] has centered on the theory that Kaposi's sarcoma is the expression of a reaction of the reticuloendothelial system to an agent,

the nature of which is still unknown, capable of stimulating an hyperplastic, dysplastic, or neoplastic type of growth. The appearance of widely separated lesions in crops supports the concept of a systemic disorder. Kaposi,[76] in his original article, spoke in terms of a "dyscrasia." Similarly, Dörffel[34] expressed the view that the multiple lesions are independent and autonomous and not metastases. The probability that the tissue primarily involved is the reticuloendothelial system is furthered by the occasional coexistence of Kaposi's sarcoma with lymphatic or myelogenous leukemia,[27,43,71,115,130] Hodgkin's disease,[52,83,94] mycosis fungoides,[81,136] Brill-Symmer's disease,[83] and lymphoblastoma.[83] Epstein[41] has recently emphasized this relationship, with particular stress on the association of Kaposi's sarcoma and lymphoblastoma. Although present evidence does favor the concepts that the disease is of a systemic nature and that it originates in the reticuloendothelial system, there is a difference of opinion as to the cell of origin. Endothelium, perithelium, plasma cells, fibroblasts, and periadventitial mesenchymal cells have been variously considered as the cells primarily involved in the process.

Any consideration of the reactions of the reticular tissue rests upon the knowledge of its normal cytology and upon the relations interceding between the individual elements. Unfortunately, the whole concept of the system was born from the demonstration that it possesses metabolic functions and from the observation of its reaction to vital dyes or particulate material. Therefore, it cannot be identified upon a strictly cytological basis. As Marshall[87] says, "The reticuloendothelial system is not a distinct cytological entity, but a functional state of some metallophilic cells, due either to the properties of the cells themselves or to the nature of the local blood and lymph circulation." He points out that this has unavoidably led to a confusion of terms. Thus, within the frame of the reticuloendothelial system Maximow describes two types of cells, one phagocytic and dye-staining and the other nonphagocytic and non-dye-staining, but the latter are provided with many potential lines of development. Jaffe names *reticular cells* what Maximow calls *undifferentiated cells*, and Masugi speaks of *resting reticuloendothelial cells* as *primitive multipotent cells*. The terms *reticulum cell*, *histiocyte*, and *clasmatocyte* are used synonymously by Jackson and Parker, and finally other investigators (particularly of the Italian school) describe the histiocyte as a cell capable of transformation into many other cell types, including the fat cells and the cells of the hematopoietic system (Marshall[87]).

It is obvious that the morphologic method, as applied to the study of the reticuloendothelial system, has been carried far beyond its justifiable limits. Any attempt to identify cell types or to trace transitions of one cell into another in tissues which have been processed according to the usual microscopic techniques is unavoidably met with the limitations that are inherent in the method.

What is true for normal cells is even more so for cells mobilized by abnormal stimuli. For these reasons, it cannot be expected that cytologic observations on tissues processed by routine methods will provide the solution to the problem as to the type of cell primarily involved in the Kaposi lesion. As McCarthy and Pack[83] have indicated, perhaps the solution will not materialize until results of tissue cultures of early lesions should become available. Although these results are not conclusive, preliminary investigations along this line by Osborne et al.[94] seem to indicate that the lesion springs from a disorder of the primitive mesenchymal cell.

This is well in keeping with the morphology of the lesion, basically consisting of a proliferation of varieties of connective tissue cells, of sinusoidal spaces carrying blood, and of lymph channels. A growth with such pleomorphic characteristics must necessarily originate from a cell with mul-

tiple developmental potentialities, which might well be identified with the primitive reticular cell (synonyms: cell of the undifferentiated reticular syncytium, undifferentiated mesenchymal cell).

4. Clinical Aspects

Prior to Dörffel's study, in 1932,[34] it was generally acknowledged that Kaposi's sarcoma was primarily a disease of the skin and subcutaneous tissue and that the later-appearing visceral lesions were metastatic. Since then, several cases have been reported indicating that the viscera may become involved prior to, or unassociated with, any skin manifestation. The identification of these cases as instances of visceral Kaposi's sarcoma is justified by the close resemblance of the lesions to those usually seen in the skin. This further supports the concept that Kaposi's sarcoma is a systemic disease of multicentric origin, likely to involve independently and in an unpredictable manner, simultaneously or successively, skin and internal organs.

The clinical manifestations of the disease can be divided into two main categories: 1. diagnostic and 2. presumptive.

1. *Diagnostic Lesions.*—The cutaneous manifestations of the disease are so typical that in general they can be diagnosed upon inspection. They are characterized by irregularly shaped light-red or bluish-red or reddish-brown well-demarcated painless macules which may vary in size from a few millimeters to 2 or 3 cm. in largest dimension. As the process advances, the macules enlarge and become elevated, nodular, and indurated; they darken in color so as to simulate in their appearance a malignant melanoma. Only a single lesion or a few lesions can be present[127] or as many as 450, as in one recorded case.[5] The lesions show a tendency to coalesce into large macules, nodules, or plaques, often 20 cm. or more in size. Purpuric discoloration and telangiectasis can be noted between the lesions or in the skin overlying the lesions.[88] Bullae simulating cysts and bleeding ulcers often develop in the aging lesions.

In the early course of the disease the lesions tend to be unilateral, usually in one hand or foot, or in one of the upper or lower limbs, but soon they extend to involve symmetrical areas in the other extremity, to use the expression of McCarthy and Pack,[83] "in stocking or glove fashion" (Fig. 1). Later the process spreads centripetally to the trunk and face and lesions may appear in the visible mucous membranes. Although this is the usual sequence of events, the process may originate in any part of the body and extend in disorderly fashion.

Since the basic lesion has not a static nature and the disease is often of long duration, with remissions and reactivations, fresh and old lesions can coexist, resulting in a marked pleomorphism of gross manifestions.

Fig. 1.—Symmetrical edema of hands and feet with early Kaposi's lesions in a 32-year-old white American man. The edema had been present for four years in the feet and for a somewhat shorter interval in the hands. The diagnostic lesions, however, had only been present for one year.



Contrary to Kaposi's expectation, secondary involvement of the internal organs is not frequent, occurring only in about 10% of the cases. Among the viscera, the alimentary tract, from mouth to rectum, is the most frequently affected. Diarrhea, gastroenterorrhagia, and hemorrhagic effusions into the abdominal cavity are associated clinical manifestations. Unique is the case of Sherwin and Gordimer,[120] in which the process had extended from the mesentery of the small bowel into a loop of bowel, giving rise to the formation of a large intra-abdominal air cyst which was visualized in roentgenography.

Liver, lungs, superficial and deep lymph nodes, spleen, and marrow can also be involved, and circumscribed areas of osteoporosis have been described in conjunction with bony localization.[21]

The involvement of the viscera usually follows the cutaneous manifestations; however, as mentioned, the reverse situation may take place: In a case of Pearce and Valker[99] a nodule on the gum was noticed several months before the skin became involved. Barringer and Dean[7] reported two cases in which the first lesion appeared on the glans penis. Both in the cases of Goldschlag[50,51] and in that of Van Cleve and Hellwig[131] the initial manifestations of the disease were in the inguinal lymph nodes. Intestinal symptoms developed many months before the cutaneous manifestations in a case of Paolini,[97] and pharynx and larynx were primarily involved in a case of Bilancioni.[15] Evidence has also been presented of visceral involvement unassociated with any skin manifestations.[130] Greppi and Bettoni[57] reported a case in which the only external manifestations were in the glans penis; later the inguinal lymph nodes became involved, and at postmortem examination additional nodules were found in the lungs and in the psoas muscle. In another case of Nesbitt et al.,[90] omentum, alimentary tract, heart, lungs, liver, spleen, kidneys, lymph nodes, several vertebrae, thyroid gland, and brain were involved by the process in the absence of dermal manifestations. In three cases which I reported,[130] liver, kidney, and small bowel (Case 1); mediastinum (Case 2), and lymph nodes, intestine, and liver (Case 3) were affected, and in all three instances the skin was normal. Graham[53] reported a case with ocular localization, and in a case of Seagrave's,[118] the ear, nose, and nasopharynx were primarily affected. Although apparently no organ is exempt from the disease, primary visceral Kaposi's sarcoma seems to have a particular predilection for the heart, and several cases have been recorded in which cardiac involvement was the only or the main manifestation of the process.[1,23,29,31,134]

2. *Presumptive Manifestations.*—Swelling of the extremities, usually symmetric in distribution, frequently accompanies and not rarely precedes the cutaneous manifestations. This swelling, as already indicated, must possess some significance, but in many instances it escapes a satisfactory explanation. Blockage of lymph drainage, secondary either to infiltration of the lymphatic vessels or to involvement of the regional lymph nodes, may cause the edema. Coexistent dermosclerotic changes in proximity to the cutaneous nodules may also explain the occurrence of this condition, but mechanical static factors are absent in many cases; the lymph drainage, so far as it can be ascertained, is not impaired, and in these instances the cause of the edema escapes any satisfactory explanation. Blood serum albumin levels, when determined, were often found to be normal; thus, hemodynamic factors also seems to be unimportant in this connection.

Enlargement of the lymph nodes, both superficial and deep, is also an early manifestation of the disease. Kaposi[77] was of the opinion that the lymphadenopathy was due to secondary infection resulting from ulceration of the skin lesions. Actually, it may precede the cutaneous manifestations. The enlargement does not necessarily indicate neoplastic involvement. As a matter of

fact, in several instances the only detectable change is that of a nonspecific type of reactive hyperplasia.[50,57,84]

The spleen also can be greatly enlarged. Stats [121] mentions cases in which the organ weighed over 700 gm. in which microscopic examination revealed hyperplasia of reticulum cells in the absence of any other significant change.

Likewise, several investigators have commented on the hyperplastic state of the marrow, mainly due to an increase of reticulum cells and of cells of the monocytic series.[12,121] These marrow changes are often reflected by alterations in the hemogram, mostly characterized by an increase of lymphocytes and by the appearance of atypical mononuclear cells, partly of lymphoid and partly of histioid structure.[14]

These changes in the blood and in the lymph hematopoietic organs can be explained either on the basis of a nonspecific reaction of the reticuloendothelial system which precedes or accompanies the development of the sarcoma or as a manifestation of the disease; the latter possibility is well in keeping with the developmental potentialities of the cell which probably is responsible for this condition, namely, the primitive reticulum cell.

Cutaneous hemorrhage is another early manifestation of the disease. Kaposi mentions the development of sarcomatous nodules at the site of preceding cutaneous hemorrhages in one of his cases. This occurrence has been confirmed by several investigators.[33,101,103] Telangiectatic areas have also been described in nodules and plaques and even in apparently normal skin. The cutaneous hemorrhage may be so extensive as to give rise to a generalized purpuric state in otherwise normal skin.

Kaposi's lesions have been described in areas of fading hemorrhage,[34] and some investigators [33] have suggested that the hemorrhage is the primary factor in the production of the lesions. Exposure to cold, ergotism, and primary vascular disease have been advocated to explain this hemorrhage; it has been indicated also that some products of the disintegrating red blood cells may stimulate the proliferation of local vascular endothelium and mesenchymal elements and thus initiate the development of the lesion.

This hypothesis might apply to the origin of the cutaneous nodules, but it does not explain as well those occurring in mucous membranes. In fact, bleeding from the mucous membranes, to my knowledge, does not occur, unless in the presence of already established lesions.

In a case of Ravaut and Cachera [109] of Kaposi's sarcoma of the lower extremities associated with extensive calcification of the arteries of the legs and purpuric manifestations, the bleeding time was prolonged and the blood clot, nonretractible. However, according to Stats,[121] operative wounds do not bleed excessively in patients with Kaposi's sarcoma, and, according to Bluefarb,[16] the bleeding and clotting mechanisms are generally not altered in this condition.

5. The Histology of the Lesion

The microscopic aspects of the lesion reemphasize the bizarre versatility of the gross manifestations. Some classify Kaposi's disease among the granulomas; others, among the neoplasms, and the 23 different names applied from time to time to the condition [84] stress further the lack of agreement on the nature of the process.

A necessary compromise imposed by the findings is that the process may reveal itself within the frame of an inflammatory process, of a granulomatous process, or of a true neoplasia. Engorgement of blood and lymph channels and perivascular infiltration by round cells, plasma cells, and less numerous histiocytic and fibroblastic elements are the predominant features of the inflammatory pattern. When numerous macrophagic histiocytes and fibroblasts are present and there is associated proliferation of blood and lymph channels, the structure of the lesion mimics that of a nonspecific type of granuloma. In the neoplastic

pattern, the aspects of the lesions vary according to the cellular elements predominantly involved. If vascular proliferation prevails, the lesion will resemble an angioblastic type of growth; if, instead, lymph channels are predominant, the appearances of the lesion will not be dissimilar from that of a lymphangioblastoma; excessive and disorderly proliferation of immature fibroblastic elements and mesenchymal cells will duplicate the structure of a fibrosarcoma or of a reticulum-cell sarcoma.

Incidental to the imperfect closure or the weakness of the walls of the newly formed blood channels, extravasation of red cells and deposition of hemosiderin pigment occurs, giving rise to characteristic, but not pathognomonic, features of the lesion. In fact, hemosiderin pigment may be absent in the lesion, a point well stressed by Pollitzer.[104]

Since the histology of the process is so varied, one feels the necessity of selecting a common diagnostic denominator, and this can be found in the symbiotic proliferation of angioblastic elements and of mesenchymal cells. If this be accepted, it becomes clear that variations in the appearances of the individual lesions merely reflect quantitative and qualitative differences in the rate of growth and maturation of the two basic components. Whenever cellular differentiation proceeds harmoniously, and with fairly well balanced proliferation of angioblastic elements and mesenchymal cells, the resulting pattern will be that of a hyperplastic, inflammatory, or granulomatous type of growth. With loss of this organizing power, a dysplastic type of growth will take place, provided with the aggressive potentialities inherent in a malignant process.

A certain degree of correlation has been advocated between microscopic structure and gross appearance of the lesion "as it evolves from an inflammation-like macule into the 'granulomatous' bluish-red nodule resembling an angioma, and into the final black plaques of frank sarcoma." [83]

This implies that the lesion undergoes a kind of cycle and that it progresses from an inflammatory phase to a neoplastic phase, through an intervening granulomatous phase.

This temporal sequence of events is well substantiated by clinical, as well as by pathological, evidence, but in many instances a clear line of demarcation between "phases" cannot be drawn, and this is a problem of more than academic importance, for it has considerable bearing on prognosis.

I was faced with a problem of this sort some years ago [130] at the examination of a mediastinal mass, interpreted as consistent with Kaposi's lesion, in a 65-year-old American-born white woman, dying of myelogenous leukemia. In some areas the mass was composed of endothelial-lined sinuses, endothelial sprouts, and pleomorphic but well-differentiated mesenchymal cells, and all this was well in keeping with a nonspecific type of granulomatous process. On the other hand, in some other areas there was disharmonic proliferation of angioblastic structures and many connective tissue cells showed atypicalities, hinting that the growth had aggressive potentialities. While in this case the decision as to the benign or malignant nature of the process was merely of academic interest, if an actual diagnostic problem were involved, the pathologist's resolution could be made only with difficulty.

The occurrence of different histological patterns in coexisting anatomically independent lesions observed at the same time is another confusing possibility. This eventuality is illustrated by Figure 2*A*, *B*, and *C*, showing in the given order the structure of a hepatic, an intestinal, and a renal lesion. All three lesions have been interpreted as visceral manifestations of Kaposi's disease and were accidentally discovered at postmortem examination in a 59-year-old Italian laborer dying of hypertensive heart disease with congestive

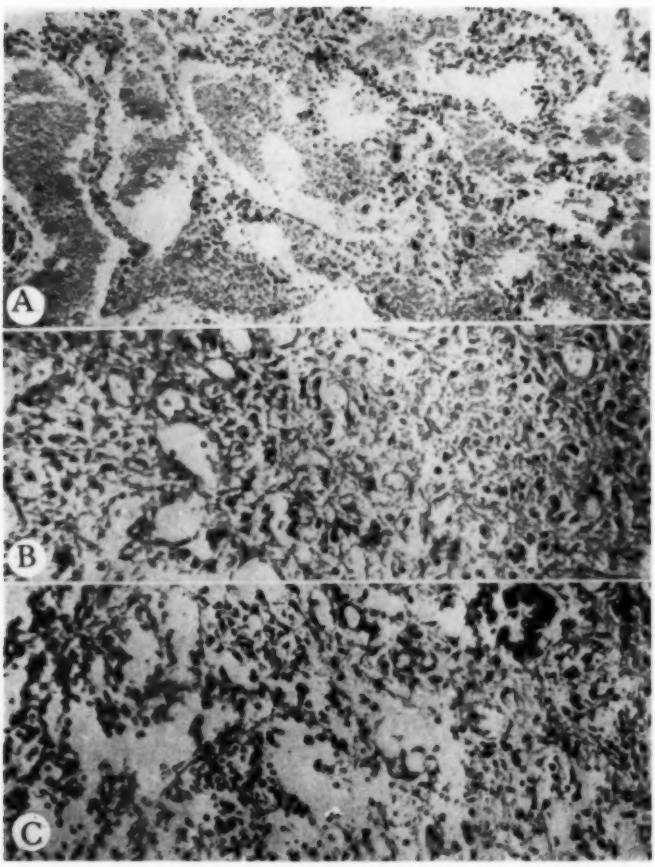


Fig. 2.—Variations in histological pattern in anatomically independent lesions observed at the same time. *A*, nodule in liver, showing well-differentiated angioblastic structure. *B*, nodule in the small intestine, displaying a granulomatous pattern. *C*, renal nodule with disorderly proliferation of endothelial-lined sinuses and pleomorphic mesenchymal cells arousing suspicion of malignant change. A 59-year-old Italian laborer who died of hypertensive heart disease with congestive failure. There were no skin manifestations. Reproduced from Tedeschi, C. G.; Folsom, H. F., and Carnicelli, T. J.: *Arch. Path.* 43:335-357 1947.

failure.[130] Notice the well-differentiated angioblastic structure of the hepatic nodule (*A*), as contrasted with the granulomatous pattern of the nodule in the intestine (*B*) and with the disorderly proliferation of endothelial cells, vascular channels, and pleomorphic mesenchymal cells of the renal nodule (*C*), arousing suspicion that a malignant change has taken place in one of three anatomically independent lesions observed at the same time. Since these three lesions were discovered at autopsy and all of them had been asymptomatic, there are no bases in this case to construe a correlation between the chronologic appearance of the lesions and their structure at the time of observation.

Although it is generally agreed upon that the lesion of Kaposi's sarcoma is not, in most instances, of a morphologically predetermined nature, cases are on record which seem to indicate that in some particular instances the lesion carries from its start the "genes" of its benign or malignant potentialities. This contention is based on the occurrence of rapidly fatal cases of the so-called d'emblée variety,[18] in which early examination of the lesion already reveals frankly sarcomatous patterns, in contrast to slowly progressing cases in which repeated tissue biopsies over the period of years disclose that the lesion is retaining its original inflammatory or granulomatous characteristics, in the absence of apparent evolutionary changes.

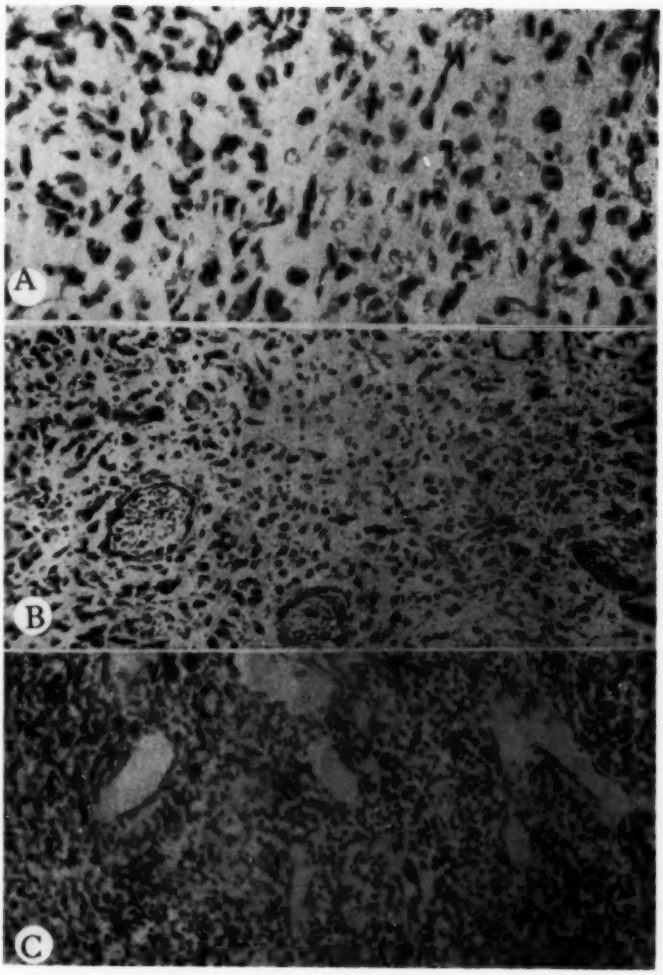
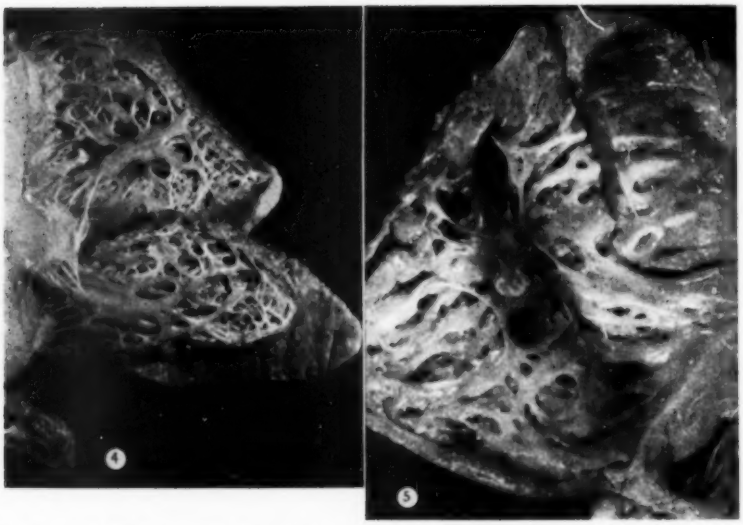


Fig. 3.—*Ab initio* sarcomatous pattern of Kaposi's lesions (so-called d'emblée variety) in 17-year-old white American youth. *A*, rapidly enlarging cervical lymph node, first diagnosed as reticulum-cell sarcoma (biopsy). *B*, intestinal lesion at postmortem examination, showing intermingling of blood channels and pleomorphic mesenchymal-cell proliferation; hemosiderin-laden macrophages are noticeable at the right and left edges of the picture. *C*, hepatic nodule, displaying symbiotic proliferation of poorly formed blood channels and of immature mesenchymal cells, for the most part identified as primitive reticulum cells. Reproduced from Tedeschi, C. G.; Folsom, H. F., and Carnicelli, T. J.: *Arch. Path.* 43:335-357, 1947.

What probably represents the d'emblée variety of Kaposi's sarcoma is illustrated by the following case:

A 17-year-old white American-born youth died of intestinal intussusception.[189] A few weeks before his death he noticed a rapidly enlarging lymph node in the left supraclavicular fossa that was removed and examined. Additional lesions were found at postmortem examination in the intussuscepted portion of the intestine and in the right lobe of the liver, Figure 3A from the supraclavicular node, Figure 3B from the intestinal lesion, and Figure 3C from the hepatic lesion, all show a basically identical structure, namely, a symbiotic proliferation, in various proportions, of poorly formed blood channels and of immature mesenchymal cells (for the greatest part identified as primitive reticulum cells), including atypical forms and frequent mitosis. These various lesions were thought to represent multiple localizations of Kaposi's sarcoma. Since the patient had been in good health until a few weeks before the fatal episode of intussusception, it may be presumed that the disease process was of recent origin. The identity of the findings in the various localizations further suggests that the lesions had common ancestral origin and potentiality, both of growth and of differentiation.

In contrast, the next case illustrates what probably represents the *ab initio* granulomatous pattern of the Kaposi's lesion:



Figs. 4 and 5.—Specimens from the same case as Figure 1. Diffuse thickening of the mural endocardium lining the left (Fig. 4) and the right (Fig. 5) ventricle. The heart weighed 540 gm.

The patient was a 32-year-old American white postal worker who 13 years prior to admission developed a dermatosis spreading from toes to feet that cleared gradually, to return on the tip of the nose and ears. The new lesions were removed and diagnosed as erythrodermatitis. Nine years later he developed progressive swelling of feet and legs, then of arms and face, and one year ago he noted the appearance of discrete red raised round lesions below the left knee, which soon extended to the dorsum of the left wrist, the feet, the lower extremities, and the face. At this time the heart was noted to be greatly enlarged, and while at the hospital, the patient developed arrhythmias, including nodal rhythm with bradycardia, auricular fibrillation with multifocal ventricular beats, ventricular tachycardia, and ventricular standstill. He died suddenly while in the x-ray department for a chest film.

In addition to the already described skin changes, postmortem examination revealed alterations in the heart, lungs, and intestines. The heart weighed 540 gm. and showed dilatation of the chambers and some thickening of the trabeculae carneae. The myocardium was increased in consistency and displayed a mottled appearance with irregularly alternating reddish-brown and pale-gray areas and streaks of glistening tissue, suggesting fibrosis. However, the walls of the ventricles were almost within the limits of normal thickness, the right measuring 0.3 cm. and the left, 1.6 cm. The endocardium lining the left ventricle was moderately thickened in a diffuse fashion (Fig. 4). Similar areas of endocardial thickening ranging from 0.4 to 3 cm. across were present in the tip of the right auricular appendage, in the pulmonary conus (Fig. 5), and in the posterior aspect of the interventricular septum. The foramen ovale was closed; valves and coronary arteries were no remarkable. The right lung weighed 750 gm., and the left, 710 gm. The major portion of both organs showed diminished crepitation, increased consistency, and purplish blue discoloration. The gross appearance suggested extensive confluent consolidation.

Esophagus, stomach, and duodenum were not remarkable, but both the jejunum and the ileum and, to less extent, the cecum and the ascending and transverse colon showed mucosal changes characterized by raised moderately firm nodules and plaques, from pinpoint to 0.6 cm. across, often confluent, and ranging in color from gray-pink to deep red. The intervening mucosa was congested, with areas of hemorrhagic discoloration.

The spleen was enlarged and congested (350 gm.), and the mesenteric lymph nodes were more prominent than normally (up to 2 cm.) and rather soft, with a gray-pink color.

The other organs and systems appeared to be grossly unremarkable (permission to examine the brain was not obtained), but changes were revealed by the microscopic sections in practically every organ examined, and the final pathological diagnosis was of Kaposi's sarcoma, granulomatous phase, involving skin, myocardium, lungs, liver, pancreas, kidneys, prostate, intestines, and testis.

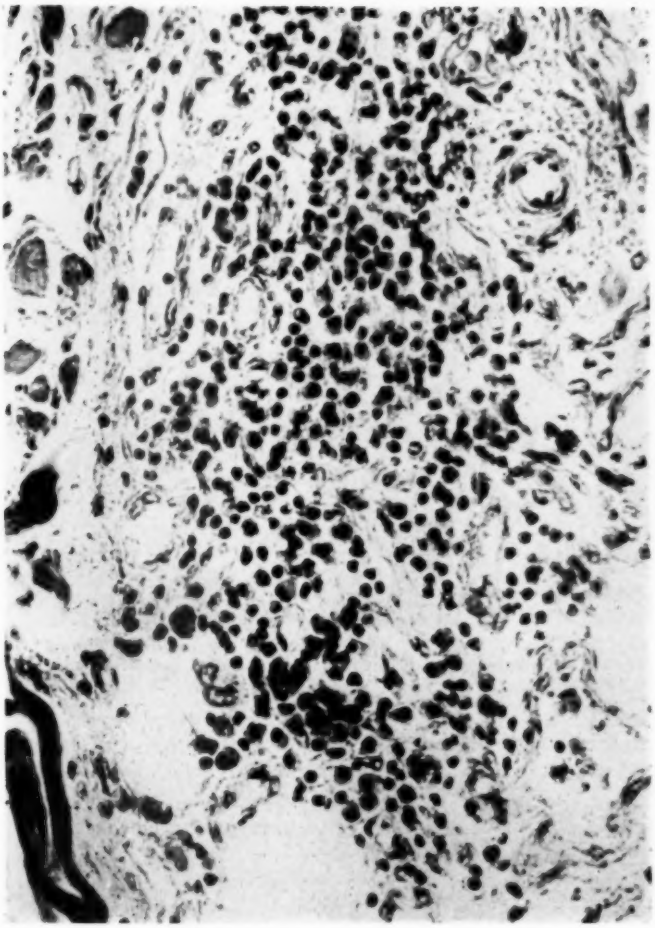
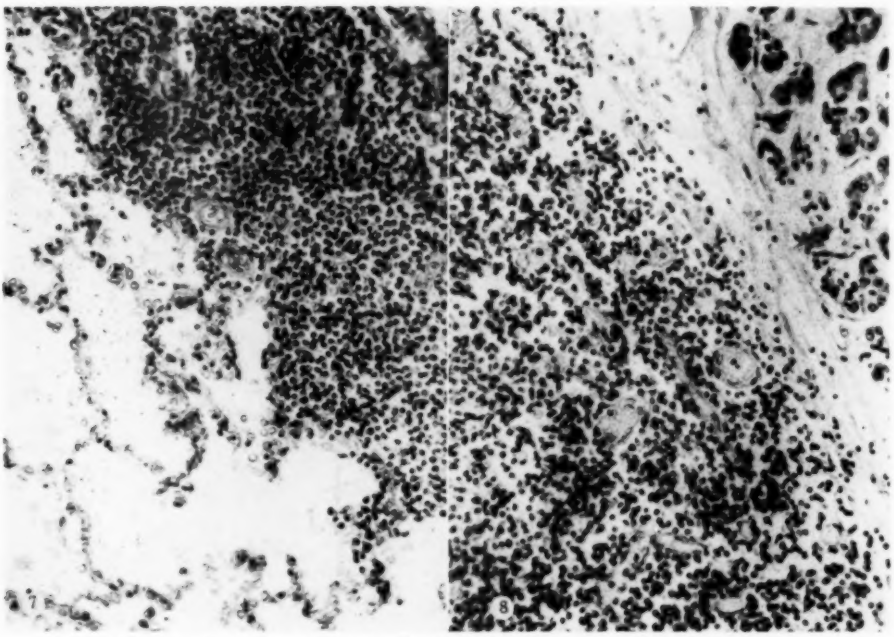


Fig. 6.—Skin biopsy specimen from the same case as Figure 1, obtained a few months before death. Notice the well-defined granulomatous pattern and the hemosiderin-laden macrophages, which are numerous at the left of the picture.

The lesions in the various localizations displayed almost identical patterns, and comparison of the biopsy slides from the skin lesions obtained five months before death and of the tissues obtained at postmortem examination showed that the process had retained its original features. Figure 6 is from a lesion deep in the dermis, obtained when the patient was still alive. Notice the irregular intermingling of blood channels, some well-formed and some poorly developed, and of mesenchymal cells. The latter include varieties of cell types, mostly lymphocytoid cells, cells with characteristics of plasma cells, fibroblastic elements, and fewer large cells, interpreted as histiocytes. Hemosiderin-laden macrophages and free-hemosiderin granules are noticeable here and there, particularly at the edges of the nodule. No mitoses were seen. Figure 7, from a lesion in the right lung, and Figure 8, from a lesion within the pancreas, duplicate the structure of the skin lesion, and identical patterns were shown by the lesions in the other localizations. Figures 9-12, from different portions of the heart, show transitions from an active exceedingly cellular granulomatous lesion (Fig. 9) to a lesion showing progressive rarefaction of mesenchymal cells (Fig. 10)



Figs. 7 and 8.—Specimens from lesions in the lung and pancreas in the same case as Figure 1, showing persistence of granulomatous pattern with predominance of lymphocytoid elements and of well-formed blood channels.

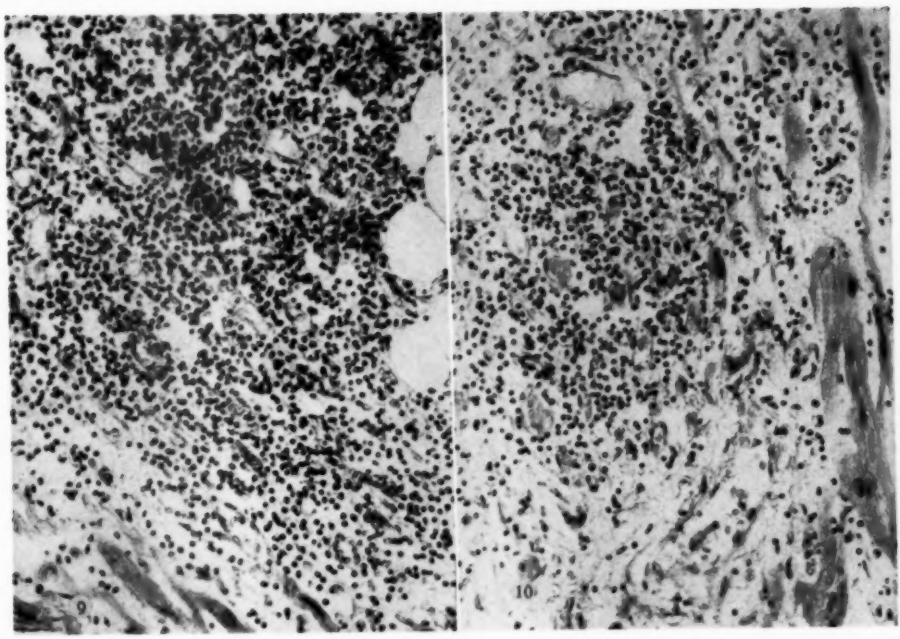
and incipient fibroblastic proliferation (Fig. 11) to an almost completely healed lesion, characterized by vascularized scar tissue (Fig. 12). Despite the favorable evolution of the lesion and the attempted regeneration of myofibers[132] (Fig. 13), large portions of myocardium underwent replacement by fibroblastic tissue, and this presumably was the cause of the disordered cardiac rhythm and of the sudden death.

Absence of mitosis, as well as of cellular atypicalities, and fairly well-balanced proliferation of blood channels and connective tissue cells, in both the lesions found before and those found after death, allocate the process to the granulomatous, rather than to the neoplastic, category of Kaposi's disease and give support to the contention that the disease started as a hyperplastic process (in contrast to the d'emblée displastic nature of the condition in the previous case). The widespread visceral involvement in this case further indicates that there is no tissue which is immune to the process. It emphasizes also the probable autochthonous origin of the lesions in the various localizations, as opposed to the concept of tumor metastasis. As in several cases of others, in this instance also no satisfactory explanation can be found for the enlargement of the spleen and of the lymph nodes, which showed nothing more than an apparent numerical increase of reticulum cells.

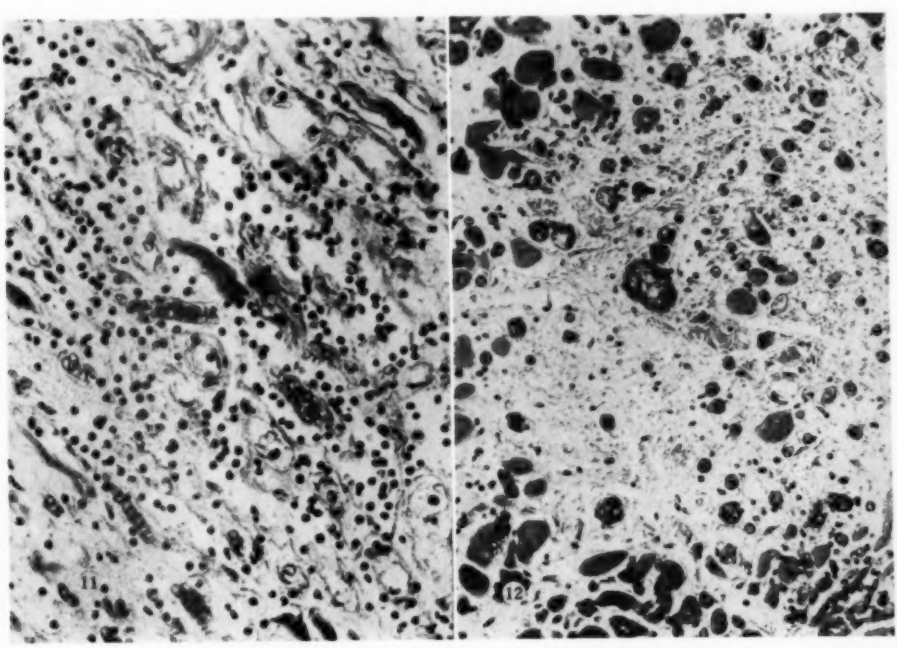
Finally, this case illustrates the point that the Kaposi's lesion can heal spontaneously. As indicated by the findings in the heart, this is accomplished through a progressive proliferation of fibroblastic tissue, resulting in scar formation, a course of events which is well in keeping with the granulomatous nature of the lesion.

6. Prognosis

The question arises at this point: Do the different structural patterns which characterize the Kaposi lesion give any indication



Figs. 9-12—Specimens from the same case as Figure 1, illustrating different phases of Kaposi lesions within the heart from active, cellular, granulomatous pattern (Fig. 9), to fading mesenchymal cell infiltration (Fig. 10), to incipient fibroblastic tissue proliferation (Fig. 11), to almost complete healing, characterized by vascularized scar tissue (Fig. 12).



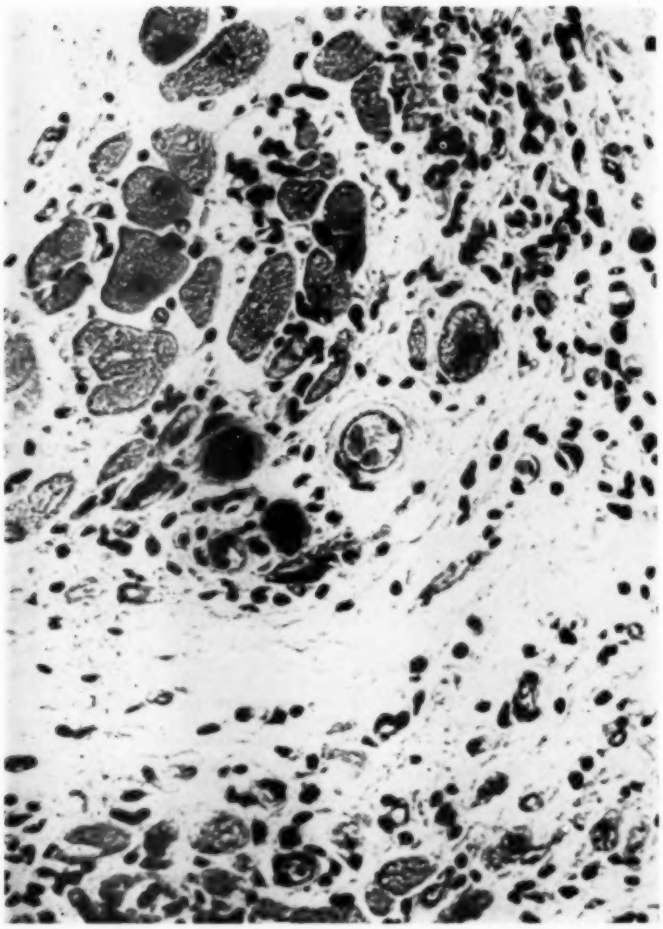


Fig. 13.—Specimen from the same case as Figure 1, showing giant bizarre nuclei in cardiac myofibers in an area of healing Kaposi lesion. This is interpreted as an attempt at regeneration on the part of the damaged cardiac muscle.

of the foreseeable clinical course and response to treatment? If so, no effort should be neglected to improve our methods of anatomical classification.

There is no way of making certain in the individual case what the outcome of the disease will be. Kaposi's [76] original interpretation was that the disease was rapidly fatal in from two to three years. Subsequently,[77] he decided that the average duration was from about 5 to 10 years. Cases are on record in which the disease runs a fulminating course, and other cases have been reported in which the patient was still alive after 25 years of active disease.[85,86,106] McCarthy and Pack [83] have given an average survival rate of eight years in treated cases, and this figure is probably representative of the general trend of the disease.

It has been said that the course is unfavorable when both extremities are affected and there is associated edema, inasmuch as this indicates involvement of deep structures. The detection of lesions in viscera and lymph nodes is also an unfavorable sign, because it shows that the disease has spread beyond control. However, spontaneous regression of the nodules has been noted many times, and the disease is no longer regarded as invariably fatal.[58] Ob-

viously, lesions bearing an inflammatory or granulomatous pattern carry a more favorable outlook than the lesions with frank sarcomatous manifestations. This trend is well shown by our last case, diagnosed Kaposi's granuloma, in which the disease, with deceptive remissions, probably lasted 13 years and certainly, 4 years. Yet, the same case indicates that other factors besides the microscopic appearance of the lesion play a decisive role in the final outcome of the condition, namely, the extent of the visceral involvement and the nature of the organs involved. Paradoxically, in this particular case, death primarily occurred from the fibrosis and scarring which followed the healing of the myocardial lesions, finally resulting in irreversible heart failure.

On the other hand, it has been shown that different microscopic patterns can be found in simultaneous crops of lesions. Therefore, the structure displayed by a particular lesion is not necessarily representative of the structural trend of the process as a whole. However, the persistence of lesions with the same characteristics over a period of time and the simultaneous detection of lesions in the same phase of differentiation indicate that the disease may carry, from the start, the stigma of its benign or malignant nature.

7. The Hemangioblastic Component of Kaposi's Sarcoma and Its Relations to Angiosarcoma

A widely accepted view is that Kaposi's sarcoma is an angiomatosis arising from embryonal vascular cells and that the lesions are autochthonous rather than metastatic. Pautrier and Diss [105] allocated the vascular disorder in the neuromyoarterial apparatus, including Schwannian elements and tactile corpuscles of Wagner-Meissner type, and express the view that Kaposi's sarcoma is to the vascular system what von Recklinghausen's disease is to the nervous system. Similarly, Hudelo [70] speaks of Kaposi's disease as an angiomatosis combined with a proliferation of the Schwann cells. Nödl [92] advocates a special irritability of the nerves supplying the blood vessels, resulting in dilatation of terminal vessels and subsequent diapedesis.

Aegerter and Peale [1] have classified the lesion of Kaposi's sarcoma among the angioid tumors and locate the primary lesion in the vascular endothelium, a view shared by several investigators.[12,46,48,91] To use Aegerter and Peale's own words, "If the endothelial lining of the normal blood vessel is the specialized product of its fibrous wall, or perhaps better, if the fibrous wall is the product of the primitive endothelial tube, it seems sensible to regard the Kaposi's sarcoma as a cancer." Dörffel [34] describes the endothelial cell lining the sinuses as breaking away to form solid cellular masses and finally becoming spindled so as to resemble fibroblasts.

Sachs et al.[114] suggest that glomus tumor, granuloma pyogenicum, and Kaposi's sarcoma are all angioblastomas. Businco [19] allocates Kaposi's sarcoma among the reticuloendotheliomas and because of the two main components of the lesion, angioblastic and reticuloendothelial, approves of the label proposed by Radaeli [108] and Serra [119] of *hemoangiocndothelioma*.

Other genetic possibilities related to vascular structures include the endothelium lining perivascular lymph channels,[103,117] the muscularis of the adventitia,[44,45,122] and the perithelium.[9,10,63,65]

According to Kusnezow,[79] the Kaposi lesion is an endoperithelioma resulting from unbalanced proliferation of the endothelium and of the perithelium of the capillary nests of the corium, under the influence of an unknown factor. In Gryzbowski's [60] opinion, the lesion is essentially an angioma arising from the proliferation of preexisting blood vessels. However, he objects to the classification of the process among the endotheliomas and the peritheliomas because perithelium and endothelium are not the only elements involved in the lesion.

Some others have introduced the concept of a polyvasculitis,[109] not too dissimilar

from polyarteritis nodosa, followed by a multifocal angiomatosis.[26]

It has been also suggested that the lesion arises on the ground of an inherited or acquired vascular debility. Cases are on record in which structural and functional changes in blood vessels were shown both in proximity and at a distance from the lesions.[12,13]

This concept is well in keeping with observations of early students of the disease that the Kaposi lesion is inclined to occur in proximity to ectatic, sclerosed, and coiled veins.[37,76,77,85,86] Dörffel[34] has further brought attention to the not infrequent finding of deposits of iron pigment in proximity to engorged dilated blood channels in the vicinity of early lesions; hence, his belief that the initial pathologic feature of the process is "hemorrhage in the *cutis*, from one or many vessels at different depths in the *cutis*."

McCarthy and Pack[83] have brought out evidence indicating that Kaposi's sarcoma and angiosarcomas have interesting parallels in anatomical distribution and behavior. From the aforementioned it is apparent that the two conditions have several similarities; however, when compared on structural ground each has distinctive characteristics of its own. There is no need to consider here the vascular hamartomas, since they are not tumors. Actually the two groups of angioblastic growths to which Kaposi's sarcoma bears some resemblance narrows down to the intracapillary and to the extracapillary types of angiosarcoma.[17,128]

The former is characterized by congeries of atypical, frequently anastomosing, capillaries lined by swollen, rounded, or elongated endothelioblasts, often heaped up so as to fill the lumens. Upon overgrowth of endothelial cells the nature of the tumor may become obscured by the presence of solid cords and sheets of anaplastic cells, mimicking the appearance of a well-vascularized sarcoma. Nevertheless, silver reticulum impregnation will disclose, even in these cases, that the tumor cells lie inside the reticulum sheath encasing each channel, an important diagnostic point well stressed by Stout,[124] Landing and Farber,[80] and others. Blood-borne metastases can be expected to occur in a growth in which the tumor cells are in direct contact with the circulating blood, and since this is often the case, the resulting lesions may simulate in their gross appearances the manifestations of Kaposi's hemorrhagic sarcoma.

In the extracapillary type of angiosarcoma there is also angioblastic proliferation, but the tumor cells are gathered outside of the channel walls and the endothelium does not participate in the growth. Tumors with these characteristics are thought to take origin from periadventitial cells, which might be identified with Zimmerman's pericyte or with Marchand's periadvential cells of the reticulum. The resulting picture again may mimic the lesion of Kaposi's sarcoma, and since in both types of angiosarcomas hemorrhage, deposition of hemosiderin pigment, and macrophagic mobilization (which are characteristic features of the Kaposi lesion) may occur from the rupture of poorly formed blood channels, these additional similarities make more difficult the task of differentiating these closely related conditions.

Orsós[93] has advanced the opinion that all vascular growths originate from the angioblast in turn, an offspring of the totipotent embryonal reticulum cell. The term "angioblast" implicitly restricts the developmental potentialities of this type of cell to the formation of structures which are related to the vascular channel. This developmental potential is well shown by the behavior, both of the intracapillary and of the extracapillary hemangioendothelioma, in which the basic cell responsible for the growth, namely, endothelium and pericyte, multiply within the limits of their restricted potentialities, giving rise either to cords or sheets of solid or canalized endothelial cells (intracapillary hemangioendothelioma) or to mantles of pericytic cells outside the walls

of the blood channels (extracapillary hemangioendothelioma).

In contrast to the restricted developmental potentialities of the two cell types, endothelium and perithelium, which are responsible for these vascular new growths, the ancestral cell of the Kaposi lesion, in order to form both vascular channels and mesenchymal cells, and among the latter varieties of cell types, must necessarily possess totipotentiality, such as the immature reticular cell does.

The distinctive characteristics of a vascular growth, more exactly of an intracapillary type of hemangioendotheliosarcoma, are shown by the following case, introduced here for comparison with the Kaposi lesion of the previous cases:

A 21-year-old white man noted in January, 1956, a painless lump in the scalp that was removed and diagnosed as hemangioendotheliosarcoma. He was given a course of 15 x-ray treatments and remained well until about 10 weeks before admission, when he began to notice the insidious onset of swelling of the ankles, anorexia, weakness, and palpitations, with dyspnea on exertion and orthopnea. On admission the heart was found to be greatly enlarged, and two small, firm subcutaneous nodules, each 0.5 cm. across, were noted in the scalp. A third nodule, slightly raised, bright red, rounded, and about 1 cm. in diameter, was seen in the posterior pharynx. About two months before death the patient developed a sudden generalized convulsion that lasted about two minutes. An electrocardiogram taken immediately after the seizure showed the onset of paroxysmal auricular tachycardia. Several more generalized convulsions occurred in the next few weeks, and neurological examination showed bilateral Babinski reflexes. Patient continued to deteriorate physically; finally he became drowsy and unresponsive, and he died three months after admission and one year from the removal of the first detected tumor in the scalp.

Postmortem examination showed a large heart (1205 gm.), distorted by a solid discoid tumor mass 9 cm. in diameter and 6 cm. thick, which occupied the posterolateral wall of the right auricle. The cut surface of the tumor was deep red, with a band of yellow-gray semifirm necrotic tissue (Fig. 14). The tumor extended downward for 4 or 5 cm. in the anterior wall of the right ventricle and in three or four places had pierced through the endocardium growing into the right auricle. In addition to the tumor nodules in the scalp and pharynx, nodules were also found in the lower lobe of both lungs (Fig. 15), in the liver (Fig. 16),

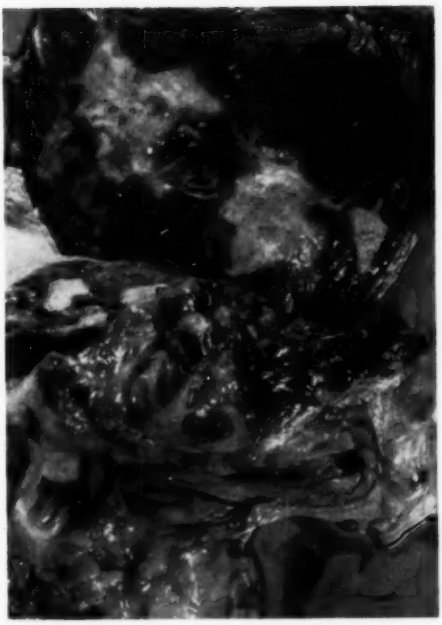
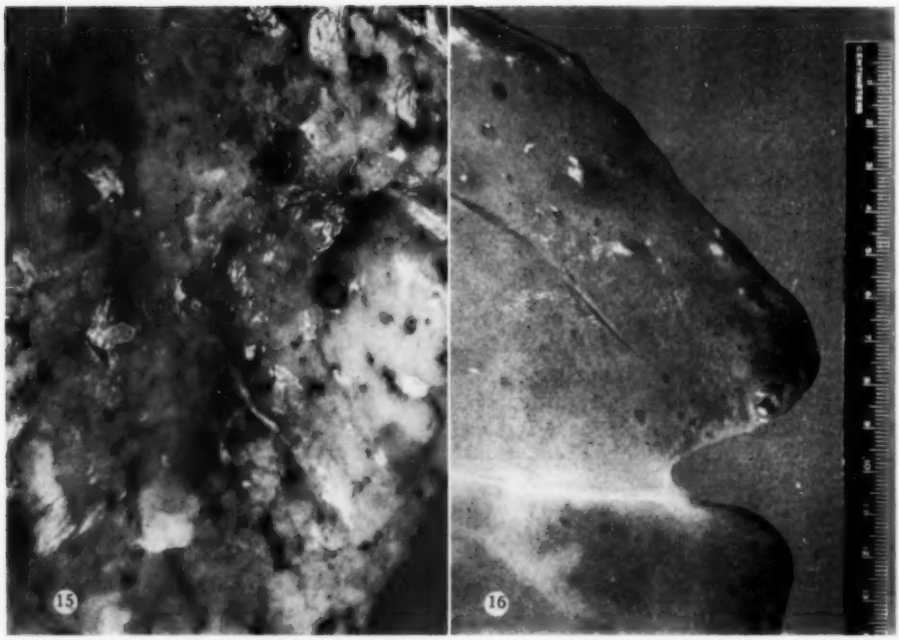


Fig. 14.—Cut surface of the tumor mass diagnosed as hemangioendotheliosarcoma in the posterolateral wall of the right ventricle in a 21-year-old white man.

and in the brain substance (Fig. 17). In all these various localizations the tumor nodules ranged in size from 0.3 to 2.3 cm., were well circumscribed, and displayed a bright red or reddish-brown color. Some of the foci have a compact structure, whereas some others had a honeycombed spongy appearance and contained blood in the individual locules.

The microscopic structure of the tumor nodules in the various localizations duplicated, with some variants, the structure of the nodule in the scalp removed one year previously. Figure 18 is from the original biopsy specimen. Notice the sheets and cords of endothelial cells, from poorly to fairly well differentiated, with attempts of canalization, often resulting in well-formed blood channels containing blood. Even in the most differentiated areas the aggressive potentialities of the growth are clearly indicated by the irregular stratification of the cells lining the lumens and their budding in solid masses. A moderate amount of fibrous connective stroma rests in between the neoplastic cells, which, although pleomorphic





Figs. 15-17.—Specimens from the same case as Figure 14, showing well-circumscribed raised bright red or reddish-brown nodules in the lung (Fig. 15), liver (Fig. 16), and brain (Fig. 17), mimicking in their gross appearance the lesion of Kaposi's sarcoma.

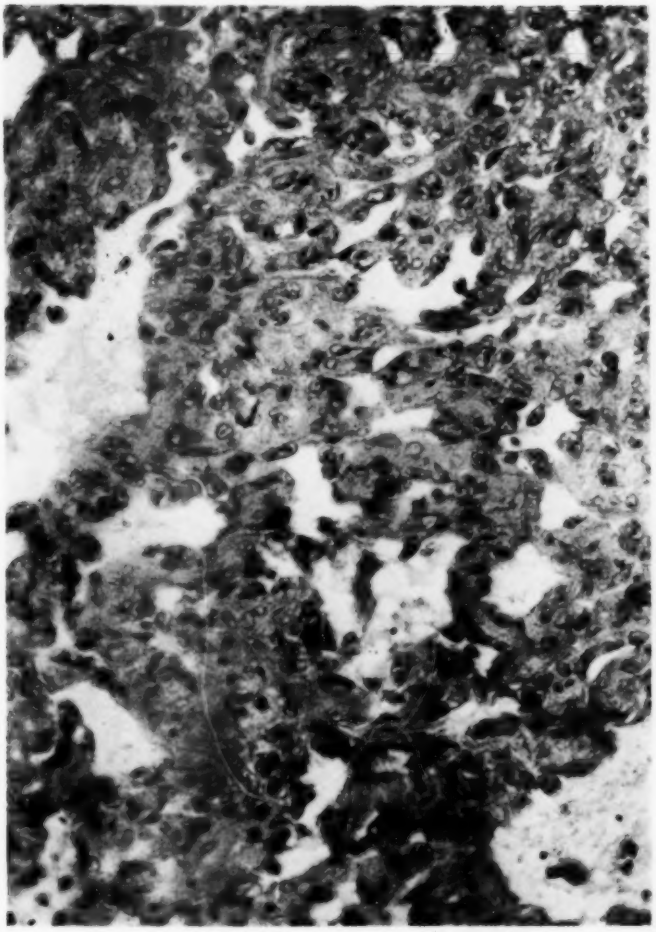
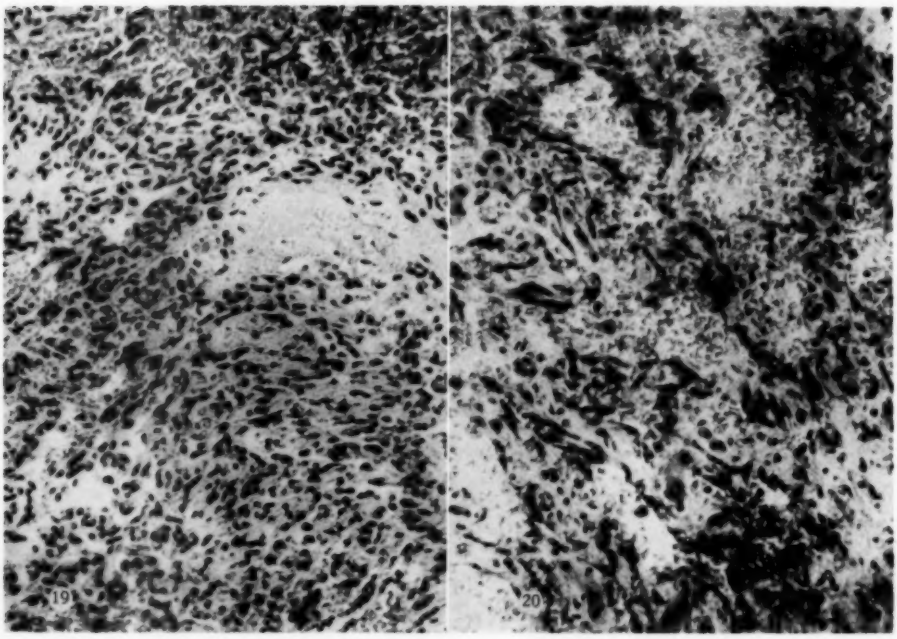
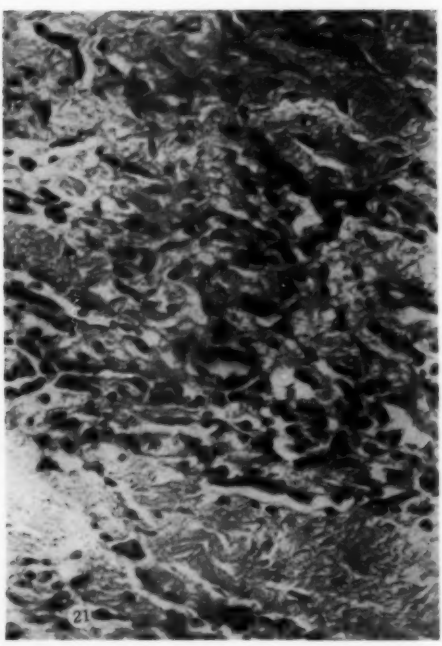


Fig. 18. — Specimen from the same case as Fig. 1, showing the structure of the nodule in the scalp removed one year previous to death. Notice the sheets and cords of endothelial cells, from poorly to fairly well differentiated, with attempts of canalization, often resulting in well-formed blood channels containing blood. Despite the marked cellular pleomorphism, the growth clearly reveals its tendency to differentiate toward a unique cell type, the vascular endothelium, and no other cell types are recognizable. This behavior contrasts with the distinctive characteristics of the Kaposi lesion, namely, symbiotic proliferation of angioblastic elements and of mesenchymal cells, of various types and in various phases of development.

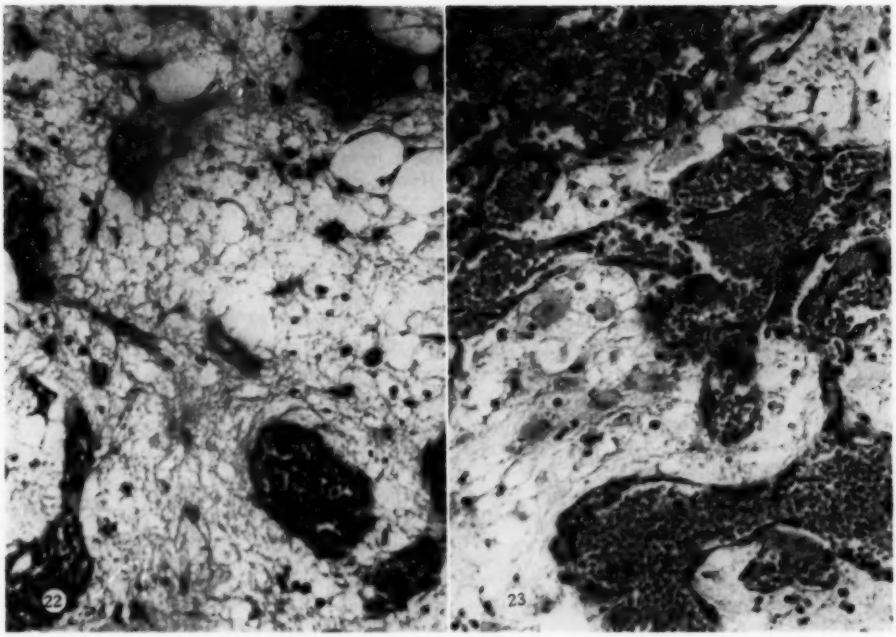
and bizarre, clearly reveal their tendency to differentiate toward a unique cell type, the vascular endothelium, and no other cell types are recognizable. The same is true of Fig. 19, from the mass in the right auricle, showing streams of endothelial cells in disorderly distribution but occasionally aligning themselves in annular fashion so as to give rise to endothelial channels containing blood. The selective tendency of the basic cell involved in the process to form primitive vascular structures is indicated by Fig. 20, from a nodule in the lung, and Fig. 21, from a nodule in the liver, both displaying well-structured blood channels containing blood. In these localizations also there is not intermingling of cell types, and the tendency of the cells to differentiate in a selective fashion into well-formed vascular structures indicates that the neoplasia sprang from a cell with restricted angioblastic potentialities. This is further emphasized by the structure of the brain nodules in which the angioblastic growth had reached such a stage of differentiation as to result in vascular structures indistinguishable from a plexiform (Fig. 22) or capillary (Fig. 23) type of angioma.

Genuine hemangioendotheliomas are rare, and this case well illustrates their distinctive





Figs. 19-21.—Specimens from the same case as Figure 14, showing the selective developmental potentialities of the cell type involved in the process in other localizations: streams of endothelial cells, occasionally giving rise to endothelial channels containing blood in the cardiac tumor (Fig. 19); primitive but clearly recognizable vascular structures in the pulmonary (Fig. 20) and hepatic (Fig. 21) nodules.



Figs. 22 and 23.—Specimens from brain nodules in the same case as Figure 14, stressing further the restricted angioblastic potentialities of the neoplasia, giving rise to vascular structure indistinguishable from a plexiform (Fig. 22) or a capillary (Fig. 23) type of angioma.

features. In this case, as in comparable cases of the literature,[8,17,20,62,107,110,124,133,138] the question arises as to whether the tumor nodules in the various localizations are expressions of blood-borne metastasis—an event well within expectation in a type of growth in which the tumor cells proliferate in actual contact with the circulating blood—or whether they represent multifocal "system" lesions, independently originated, each evolving on its own within the generic group of angioblastomata.

As McCarthy and Pack [83] say, the term hemangioendothelioma, in the clinical usage, connotes a highly malignant sarcoma. Pathologists commonly employ it to indicate both a benign and a malignant type of angiomatous growth. This reflects the difficulties that are often encountered in evaluating the actual potentialities of the neoplasia and in deciding, whenever multiple growths are present, their autonomous origin as contrasted with the concept of tumor metastasis.

The malignant nature of the growth in this case is well substantiated, both by the clinical course of the process and by the unequivocable structure of the lesions, which well fits Stout's [125] criterion of malignant growth from vascular endothelium, namely, as he says, "atypical endothelial cells in excess of the number required to line a blood channel, and vascular tubes with pronounced tendency of their lumina to anastomose." In this case, to judge from the organ most extensively involved, one in inclined to select the heart as the primary site of the malignancy. The cardiac tumor was localized in the right atrium, and this is in keeping with the generally acknowledged fact that this portion of the heart is the most frequent site of primary cardiac malignancy.[129] Angioblastic sarcomas of the heart are infrequent. De Faria [31] lists 11 cases labeled as such, 6 others diagnosed endothelioma, and 1 classified as endothelial sarcoma. Hewer and Kemp's case [69] of malignant hemangioendothelioma of the heart, with

metastasis in the liver and esophagus; the case of Gross and Englehart [59] in which the tumor diffusely infiltrated the wall of the left atrium, with no metastasis outside the heart, and Glassy and Massey's [49] case of primary cardiac hemangioendotheliosarcoma, involving endocardium and pericardium, closely resemble our own in many respects. Particularly in the cardiac localizations, a number of investigators have stressed the hemangioendotheliomatous component of the Kaposi lesion.[23,29,31] On the assumption that the precursor cell of the Kaposi lesion is the primitive reticulum cell, this is understandable, inasmuch as the cell type is endowed with full mesenchymal potencies.

8. The Lymphangioblastic Component of Kaposi's Sarcoma

Although proliferation of blood channels is one of the prominent features of Kaposi's sarcoma, lymph channels also participate in the process, and the lymphatic component of Kaposi's sarcoma may become so pronounced as to give rise within the lesion to lymphangiectatic bullous lesions, filled with lymph. Hamdi and Halil's [64] "cutaneous multiple nodular cavernous lymphangiectatic perithelioma" and Hamdi and Resat's [65] "cutaneous idiopathic multiple lymphangiectatic acroperithelioma" probably represent the lymphangiectatic and lymphoblastic variety of the Kaposi lesion. We are indebted to Pelagatti [100] for the first description of this condition (1905) and to Ronchese and Kern [113] for having revived general interest in this very unusual manifestation of the disease. These cystic lesions may vary in size from that of a pea to that of a small cherry, often communicate with each other, and when ruptured yield a profuse watery discharge or an amorphous substance similar to coagulated albumen. The gross appearances are, therefore, not too dissimilar from those of a circumscribed lymphangioma.

Several interpretations have been offered to explain this uncommon bullous manifestation. According to some investigators, the cysts are not true cysts, but excavations developing in previously solid nodules through a process of colliquation.[11,28,89] Others advanced the view that the cysts originate from stagnation of lymph, secondary to tumor pressure.[47,100,113,137] Still others have revived Pelagatti's [100] original contention that the lymphangiectases result from a neoformation of lymphatic vessels.[25,61,82,135] This problem might be answered in morphologic terms by observations noticing the presence or absence of an endothelial lining to the cyst cavities, differentiating the true cyst from the pseudocyst.

The concept of an actual new formation of lymphatic channels is well in keeping with present knowledge of the cell type primarily involved in the Kaposi's lesion, namely, a highly undifferentiated mesenchymal cell as such, able to give rise to complex lesions, unpredictably hyperplastic or dysplastic, and mainly characterized by a symbiotic proliferation in various proportions of different types of mesenchymal cells, as well as of blood and lymph channels.

9. Summary and Conclusions

Over 600 cases reported from the time of Kaposi's original description indicate that so-called sarcoma of Kaposi encompasses a wide range of clinical and pathological manifestations.

The peak incidence of the disease is between the fourth and the seventh decades of life, but the disease may occur also in children and adolescents.

The often-repeated statement that this condition predominates among people of Jewish and Italian extraction seems to need reconsideration. Should a racial proclivity actually exist, it is not clear whether it stands on a biological or a geographical basis. With increased world-wide awareness of the disease, apparent present-day racially linked characteristics might become considerably altered. The same is true for the contention that Kaposi's sarcoma is more

frequent in people of the white race than in the Negro. Present evidence indicates that Kaposi's sarcoma is probably found as frequently in the Negroes as in people of the white race.

Unchallenged remains the notion that the disease is far more frequent in men than in women, with an approximate ratio of 15:1. This may be interpreted as indicating that endocrine factors play a role in the sarcoma of Kaposi. The possibility that an endocrine imbalance may influence the occurrence of the disease is further stressed by the apparently not infrequent coincidence of Kaposi's sarcoma and diabetes mellitus.

A relation seems to exist between the occupational habits of the patient with Kaposi's sarcoma, requiring the person to stand for long periods, and the anatomical distribution of the lesions, most frequently and primarily involving hands and feet, lower legs, and forearms, often bilaterally and in a symmetrical fashion. The link between positional habits and anatomical distribution of the lesions might be found in lymphedema. Swelling of the extremities, also symmetrical in distribution, is in fact one of the early manifestations of the disease, and, as pointed out, lymphedema may predispose to the development of angioblastic malignancies.

The cause of the process is still unknown. With the reservation that Kaposi's sarcoma and Kaposi's granuloma might be two different diseases with some common manifestations, the concept that the process is caused by a systemic carcinogen, acting upon the mesenchymal tissue, is favored by the majority of the investigators.

It is also generally agreed upon that Kaposi's sarcoma is the expression of a proliferative disorder of the reticuloendothelial system. Any further attempt to identify the cell type primarily involved by the process by morphologic methods is met by the limitations that are inherent in the method. However, the pleomorphic nature of the lesion indicates that the process must necessarily originate from a cell with multiple developmental potentialities, which might well be identified with the primitive reticulum cell.

Kaposi's sarcoma is primarily a skin condition, but secondary involvement of viscera takes place in about 10% of the cases, and, although some organs are affected more frequently than others, none is immune from the disease. The involvement of the viscera usually follows the cutaneous manifestations; however, visceral involvement unassociated with any skin manifestation is a well-documented possibility.

Hyperplasia of the bone marrow and enlargement of spleen and lymph nodes are other early manifestations of the disease. These manifestations are underlined by proliferative activity of the reticuloendothelial cells. Changes in the hemogram, mostly characterized by lymphocytosis and by the appearance of atypical mononuclear cells, may also take place, but not so frequently. These alterations indicate either a nonspecific reaction of the reticuloendothelial system which precedes or accompanies the development of the Kaposi lesion or an early manifestation of the lesion.

The latter may reveal itself within the frame of an inflammatory process, or of a granuloma, or of a true neoplasia. The common diagnostic denominator is that of a symbiotic proliferation of angioblastic elements and of mesenchymal cells, and the variations in the appearance of the individual lesions merely reflect quantitative and qualitative differences in the rate of growth and maturation of the two basic cellular components involved. The lesion is not of a static nature and often progresses from the inflammatory phase to the neoplastic phase, through an intervening granulomatous phase. However, it may start with a frankly sarcomatous pattern, the so-called d'emblée variety, or it may retain its original inflammatory or granulomatous characteristics over a period of years, in the absence of apparent evolutionary changes. Since the disease is often of long duration, with remissions and reactivations, fresh and

old lesions can coexist, resulting in marked pleomorphism of gross and microscopic manifestations in simultaneous crops of lesions. This has practical prognostic implications, inasmuch as the presence of an innocent-appearing inflammatory or granulomatous lesion does not rule out malignancy in another independent lesion.

A lesion bearing an inflammatory or granulomatous pattern carries a more favorable outlook than a frankly sarcomatous lesion, but other factors, besides the microscopic appearance of the lesion, play a role in the final outcome of the condition, namely, extent of visceral involvement and nature of the organs involved. The average survival rate of eight years [83] is probably representative of the average trend of the disease. However, the process can run a fulminating course or last very many years. Healing of the lesion may take place by progressive fibrosis and scarring.

The hemangioblastic component of the lesion has led to the contention that Kaposi's sarcoma is an angiomatosis arising from embryonal vascular cells. However, in contrast to the restricted developmental potentialities of the two cell types, endothelium and perithelium—which are, respectively, responsible for the two main types of angiosarcoma, intracapillary and extracapillary—the ancestral cell of the Kaposi's lesions possesses totipotentiality, and this explains its ability to form both vascular channels and mesenchymal cells and, among the latter, varieties of cell types.

Although proliferation of blood channels is one of the prominent features of Kaposi's sarcoma, lymph channels also participate in the process, and the lymphatic component may become so pronounced as to give rise to the lymphangiectatic and lymphangioblastic variety of the Kaposi lesion.

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News and Comment

SOCIETY NEWS

New Jersey Society of Pathologists.—At the annual meeting of the New Jersey Society of Pathologists the following officers were elected for the ensuing year: Robert Brill, M.D., President; Aaron P. Gewanter, M.D., Vice-President; George L. Erdman, M.D., Secretary; J. P. Greeley, M.D., Treasurer.

The following people were appointed to serve with the officers on the executive committee: Murray Shulman, M.D.; Harold Grubin, M.D.; E. Olmstead, M.D.; Edward Fendrick, M.D.

The American Society for Experimental Pathology.—At the annual business meeting the minutes of last year's annual meeting were approved as circulated. The secretary's report was received and approved. The financial balance was $3,510.75 from the checking account and savings account at the Exchange-Security Bank in Birmingham, Ala., and the savings account at the Dry Dock Savings Bank in New York.

The membership consisted of 514 active members and 27 retired members, or a total of 541 members. There were requests for retired status from nine members; 31 new members were elected to membership, making a total of 572 (both active and retired).

The new members are as follows:

Bardawil, Wadi A.
Christie, Robert W.
Crowley, Richard V.
Davis, Richard L.
Finkel, Miriam P.
Forscher, Bernard K.
Gleiser, Chester A.
Gullino, Pietro M.
Hamilton, Leonard D.
Hellerstein, Earl E.
Hume, David M.
Joel, Walter
Lazarus, Sydney S.
Leduc, Elizabeth H.
Love, Robert
Lumb, George D.
Maddock, Charlotte L.
Monto, Raymond W.
Ortega, Louis G.
Rabson, Alan S.
Schmid, Rudi
Shanberge, Jacob N.
Sikov, Melvin R.
Smith, Albert G.
Stetson, Chandler A.
Strong, Jack P.
Townsend, Frank M.
Vazquez, Jacinto J.
Wexler, Bernard C.
Wood, Sumner, Jr.
Zimmerman, Bernard

The report of Dr. Harold L. Stewart as representative of The American Society for Experimental Pathology on the Intersociety Committee for Increase in Research Pathology Potential was received and approved. Dr. Russell L. Holman reported as the representative on the Division of Medical Sciences of the National Research Council. Dr. Robert B. Jennings reported on the Public Information activity of the Federation.

Particular thanks were expressed for the activities of these gentlemen on the respective committees, including the special expression of gratitude to Dr. Harold L. Stewart, who has asked to be relieved as representative on the Intersociety Committee.

It was pointed out that the alterations were to be proposed for membership in the Federation Board in that the Federation Board would be made up of the Past-President, the President, and the Vice-President or President-Elect of each of the six societies, assuring three year's experience for each Board member. A bylaw was to be moved in the Federation Board to allow the establishment of an advisory panel to be made up of one member from each constituent society nominated by that society to advise the President of the Federation Board on urgent matters between Board meetings.

The following officers and councillors were elected for the period July 1, 1958, through June 30, 1959: President, Dr. William B. Wartman; Vice-President, Dr. C. C. Erickson; Secretary-Treasurer, Dr. J. F. A. McManus; Councillors, Dr. Jacob Furth and Dr. K. M. Brinkhous; Past-President, Dr. Emory D. Warner.

As representatives of The American Society for Experimental Pathology to various committees, the following doctors were nominated by the Council: Intersociety Committee for Increase in Research Pathology Potential, Dr. C. C. Erickson; Division of Medical Sciences, National Research Council, Dr. Russell L. Holman; Representative to U. S. Committee for International Intersociety Pathology Committee, Dr. Harold L. Stewart.

Some discussion was raised concerning the possibility of circulation or notification of the Society member as to whether or not his paper had been accepted and if so what time and part of the program it was to appear. It was requested that the Secretary investigate the possibility of printing a separate program for the Pathology Society, or members may be asked to send in a self-addressed card on which the time and session of the presentation may be indicated. It was suggested that one of the Intersociety Sessions might be on the gastrointestinal tract.

In the Federation Board meeting, subsequent to the meeting of the Pathology Society, the alterations in the bylaws setting up the new type of Federation Board and the Advisory Council or Panel were made.

Subsequently, at a secretaries' meeting, the title "Tumors" was dropped from the Intersociety Sessions and "Cytology" was added, as well as "Immune Reactions." The Pathology Society will be responsible for setting up the Intersociety Session on Cytology, and it is hoped to have as broad a coverage of the subject as possible. Members of the Society may be asked to serve as a program committee with the Secretary.

The dinner of the Society was a striking success. One hundred twenty-one persons, by far the largest number at a Pathology Society dinner to date, were fed. The Parke-Davis Award to Dr. Emmanuel Farber was presented at the dinner.

Dr. Douglas H. Sprunt, Chairman of our Award Committee, will be asking early in the fall for nominations of the Third Annual Parke-Davis Award, and members should keep in mind younger experimentalists, under the age of 40, who might be nominated for this honor.

The fall letter will provide further news of the Society as well as announce the date for receipt of abstracts. Next year's meeting is to be in Atlantic City, N. J., the week of April 12. The Pathology Society will probably be meeting on April 14, 15, and 16, 1959. Headquarters hotels and other details will be circulated in the fall letter.

International Academy of Pathology.—The following officers were elected at the 47th annual meeting of the International Academy of Pathology: Dr. Chapman H. Binford, Washington, D. C., President; Dr. Robert E. Stowell, Kansas City, Kan., President-Elect; Dr. Frederick W. Wiglesworth, Montreal, Vice-President; Dr. F. K. Mostofi, Washington, D. C., reelected to a three-year term as Secretary-Treasurer.

Three new members were elected to the executive council: Dr. George J. Cunningham, London; Dr. Benjamin H. Landing, Cincinnati; Dr. J. Lowell Orbison, Rochester, N. Y.; Dr. Thomas D. Kinney, Cleveland, reappointed to a three-year term as editor of *Laboratory Investigation*.

American Association of Immunologists.—Officers elected for the coming year by the American Association of Immunologists are as follows: Dr. Joseph E. Smadel, Bethesda, Md., President; William C. Boyd, Ph.D., Boston, Vice-President; Dr. Calderon Howe, New York, Secretary-Treasurer.

ANNOUNCEMENTS

Training Grant in Neuropathology.—A training grant in neuropathology has recently been awarded to the Laboratory of Neuropathology of the Langley Porter Neuropsychiatric Institute, University of California School of Medicine, by the National Institute of Neurological Diseases and Blindness of the National Institute of Health. The purpose is to afford such specialized training to residents in general pathology and in neurology which can be utilized in a career of neuropathology. Applications for traineeship are to be addressed to Dr. N. Malamud, Director of the Laboratory of Neuropathology.

PERSONAL

Doctors Receive Bertha Goldblatt Teplitz Award.—The Bertha Goldblatt Teplitz Award by the Ann Langer Cancer Research Foundation of Chicago has been established "for meritorius investigation by a scientist under 45 in the field of cancer." The first recipients of the award were Dr. Charles Heidelberger, of the McArdle Memorial Laboratory for Cancer Research, of the University of Wisconsin, and Dr. David Pressman, of the Roswell Park Memorial Institute, of Buffalo.

Appointment for Dr. John R. McDonald.—Dr. John R. McDonald, formerly head of a section of surgical pathology at the Mayo Clinic, became director of pathology at the Harper Hospital, in Detroit, on July 1.

Appointment for Dr. Bernard M. Wagner.—Dr. Bernard M. Wagner has been appointed to the Robert L. King Chair for Cardiovascular Research in the Department of Pathology of the University of Washington School of Medicine. Dr. Wagner's position as Director of Pathology, Children's Hospital of Philadelphia, is being taken by Dr. William C. Yakovac.

GENERAL NEWS

Seminar on Liver Diseases Held.—A Seminar on Liver Diseases conducted by Dr. Edward A. Gall, of Cincinnati, was held in July, 1958, at the Department of Pathology, Faculty of Medicine, University of San Marcos, Lima, Peru. It is the hope of the Department that such seminars may become an annual feature of their educational program.

Medical Exchange Team.—The Unitarian Service Committe announces the sponsorship of a Medical Exchange Team to conduct a series of seminars on immunopathology in various European cities in the summer. The team acted under the chairmanship of Dr. Lewis Thomas, of the Department of Pathology, New York University College of Medicine, New York. Associated with him were Dr. Chandler A. Stetson Jr., Department of Pathology, New York University College of Medicine, New York; Dr. Frank J. Dixon, Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh; Dr. Baruj Benecerraf, New York University College of Medicine, New York; Dr. Robert Good, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, and Dr. Ernest Witebsky, Department of Bacteriology and Immunology, University of Buffalo School of Medicine, Buffalo.

Books

Introduction to Bacterial Physiology. By C. E. Clifton, Ph.D. Price, $8.50. Pp. 414 McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

This book presents a broad, yet rigorous, discussion of the very important field of bacterial physiology. It is presented from a fundamental viewpoint that should be equally pertinent to everyone who is concerned with controlling the growth and metabolic activities of bacteria. However, the final three chapters ("Physiological Aspects of Infection," "The Bacteriophage," and "Chemotherapeutic Agents") should be of particular interest to medical microbiologists.

The book is written for readers having some preparation in biochemistry, organic and physical chemistry, and bacteriology. Thus, the chapters on energetics, kinetics, and equilibria; surface chemistry; the bacterial cell, and enzymes seem superfluous. Also, the material in these chapters is presented so concisely that it would be of little value to the reader who does not have an adequate background. If this material were omitted, the chapters that relate more directly to *bacterial* physiology could have been expanded and enriched. However, in its present condition, it should be a very suitable text and reference book to accompany a lecture course on this topic.

The Healing of Wounds. Edited by Martin B. Williamson, Ph.D. Price, $7. Pp. 202, with 42 illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1957.

This little booklet embodies papers given at the Symposium on the Healing of Wounds, held at the Stritch School of Medicine of Loyola University, Chicago. A dozen contributors dealt with such problems as the metabolism of proteins and amino acids during wound healing, the role of the ground substance in wound healing, and the parts played by methionine, sulfur compounds, vitamin C, hormones, and collagen. Much of the material is experimental, but an effort was made to deal with basic problems or, as the editor, Professor Williamson, says, at the "molecular" level. Both fundamental and theoretical aspects of the problem were considered, and applications of basic information were discussed. Each section is well documented with references. The book should be stimulating to those interested in advances of basic knowledge of wound healing of the past decade.

Sekretionsstudien am Pankreas. By Priv-Doz. Dr. Volker Becker. Price, $7. Pp. 119, with 131 illustrations. Georg Thieme Verlag, Herdweg 63(14a), Stuttgart N, 1957.

This volume constitutes the first publication of a new series of monographs on subjects dealing with normal and pathologic morphology. It is edited by W. Bargmann and W. Doerr. Following a discussion of the histophysiology of the pancreas, pathologic alterations are reviewed and the essential clinical findings in chronic recurrent pancreatitis, fat necrosis, and acute hemorrhagic necrosis are fully outlined. Principal stress is laid on "dyschylia," the result of primary alteration of the production of the pancreatic secretion; on the constituents of this secretion, and on the interference with the normal flow of the secretion. Dsychylia produces "edema" of the gland, and the secreted material leaves the ducts, first causing a serous inflammation; later, fibrosis, and eventually, cirrhosis of the pancreas. By the latter is meant an increase in the connective tissue, with gradual disappearance of the lobules and regeneration of small pancreatic ducts.

This small volume gives a remarkable amount of information gained from animal experiments and autopsy observations. It is clearly written, with fifty-four illustrations, some of which are schematic drawings.

Viral Encephalitis. By William S. Fields, M.D., and Russell J. Blattner, M.D. Price, $7. Pp. 225, with 30 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1958.

This well-edited account of a symposium on viral encephalitis held at the Texas Medical Center under the auspices of the Houston Neurological Society provides a useful statement of important developments in the field since the first large epidemics of arthropod-borne encephalitis appeared in this country some twenty-five years ago. The contributors are among

those whose work has been outstanding in the area of viral infection of the nervous system. A chapter by Jordi Casals deals with the antigenic relationship of the broad group of arbor viruses, with special attention to the encephalitic varieties. E. H. Lennette covers the epidemiology of arthropod-borne viral encephalitis in North America. A section on the clinical and laboratory diagnosis of viral infections of the nervous system, by F. C. Robbins, is helpful chiefly for information about the possibilities and limitations of specific serologic diagnosis and the proper utilization of the services of the virus diagnostic laboratory. Neurologists and pediatricians will find much of interest in Knox Finley's study of the postencephalitic manifestations of arthropod-borne encephalitis. A section by H. R. Cox on the present status of preventive control of rabies and poliomyelitis is especially informative. Webb Haymaker, in collaboration with Margaret G. Smith, Ludo van Bogaert, and Coleman de Chenar, contributes a notable chapter on the pathology of viral disease in man, characterized by nuclear inclusions. Chief attention is given to acute encephalitis, both infantile and adult, with nuclear inclusions and to subacute inclusion encephalitis. By pooling experience, the authors are able to furnish a comparative pathological analysis of a considerable number of both the acute and the subacute forms. The acute cases are regarded as being of the herpes simplex type. The conclusion is drawn that subacute inclusion encephalitis and subacute sclerosing leukoencephalitis are the same disease, but the question of the nosologic and etiologic relationship of the acute and subacute forms of inclusion-body encephalitis is left open.

Diagnostic Medical Parasitology. By E. K. Markell, Ph.D., M.D., and Marietta Voge, M.A., Ph.D. Price, $7. Pp. 276, with 115 illustrations, including 5 in color. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

In the Foreword to "Diagnostic Medical Parasitology," by Markell and Voge, Dr. John F. Kessel states, "There would . . . seem to be no good reason why animal parasitology should be taught as a discipline separate from that of other infectious agents of disease." This appears, to this reviewer, to be a statement of sound principle which has been rather consistently followed by the authors of the work.

The authors are to be commended for a degree of restraint seldom seen in textbooks on parasitology. The book is short (276 pages), clearly written, and concise. Legibility in printing has not been sacrificed for these qualities. The illustrations are excellent and numerous. They include schematic representations of life cycles at appropriate places within the text together with short but clear explanations of these cycles. This should silence the objections of those who dote on life cycles to the detriment of efficient laboratory detection and identification of parasites of medical interest in clinical specimens. It is obvious that the authors have been active and interested workers in diagnostic parasitology.

This is an excellent text for medical students and medical technologists and for use as an outline from which to teach such students. It should also make a fine laboratory manual for everyday use. Although it should be supplemented by more voluminous works for reference purposes, the authors have done a first rate job of retaining the essentials of a good textbook on medical parasitology while at the same time dispensing with the superfluities.

General Pathology. Based on Lectures delivered at the Sir William Dunn School of Pathology, University of Oxford. Second edition. Edited by Sir Howard Florey, Professor of Pathology. Price, $16. Pp. 932, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

A second edition of this work appearing within four years indicates its broad appeal. New chapters have been added on tumors, arteriosclerosis, thrombosis, and metabolic changes following injury, so that the present volume provides an excellent broad coverage of general pathology. As in any book with multiple authorship, there is some uneveness in writing skill and style, but in general the presentations are excellent. Illustrations are of uniformly high quality. The book is very highly recommended. It gives the student a broad and stimulating view of biological processes in pathology.

Pathology. By W. A. D. Anderson, M.A., M.D. Price, $16. Pp. 1402, with 1294 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

When it first appeared in 1948, Anderson's "Pathology" was immediately accepted as an authoritative textbook. The collaborators included most of the outstanding professors of pathology in this country. This edition, with many of the original collaborators, continues the

same standards of excellence which characterized the first two editions. It is gratifying to note the enthusiasm that students have developed for this book, which is intended primarily as a text for medical students. It serves their purposes admirably, not only during their introduction to pathology in the second year but also during the clinical years of medical school. Though clinical-pathologic correlation is not stressed, the entire volume is written so that such correlation is easily made by the student. It is this same ease of clinical application that makes it useful also as a reference for many of the problems encountered in clinical practice by the physician. For pathologists, this book is an essential one-volume reference in their library.

The present edition represents only moderate change from the second edition. Some chapters have not been altered; others have had material added or deleted so as to emphasize more strongly current problems. A few, such as "Spirochetal and Venereal Diseases," have been completely rewritten. Bibliographies of all chapters have been brought up to date. Many illustrations have been added, and the quality of the reproductions is better than in the second edition. This edition should continue to enjoy the same popularity that the previous editions have.

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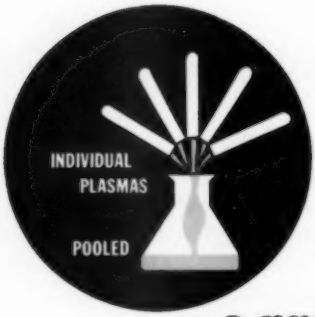
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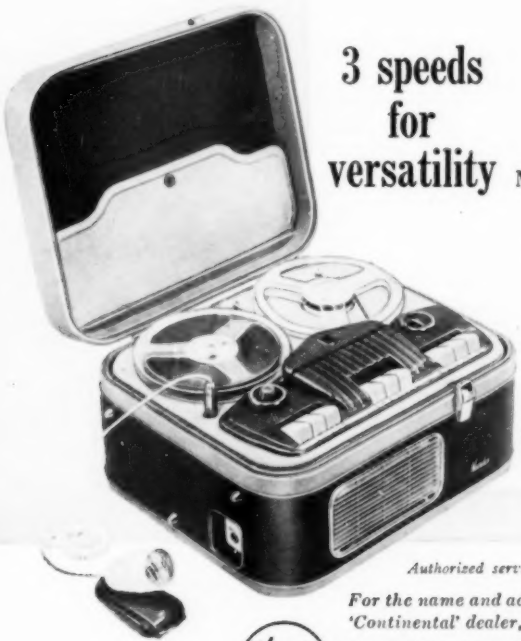


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